THE ANATOMY
OF THE
LYMPHATIC SYSTEM

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BY

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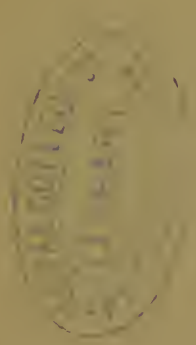

II.—THE LUNG.

LONDON:
SMITH, ELDER, & CO., 15 WATERLOO PLACE.
1875.

PREFACE.

The present volume, forming the Second Part of my work on the Lymphatic System, is, like the First Part (that on the Lymphatic System of the Serous Membranes), based on researches undertaken for the Medical Department of the Privy Council. The research was originally intended to have for its object the relation of the lymphatic system of the lung to the process of tuberculosis. It was soon ascertained, however, that our present knowledge of the lymphatics of the lungs being still incomplete, it was of great importance to subject the normal lung to a careful investigation with regard to the minute distribution of its lymphatics. The result of this investigation has proved of extreme value for understanding the process of artificial tuberculosis in guinea-pigs, as will be pointed out in the Second Section of this volume. In connection with it will be treated the process of acute miliary tuberculosis in man, for the reason that both diseases have been regarded as very similar in anatomical respects. The lung of the guinea-pig had been, as the reader may have already supposed, the chief object of study; the same organ in the dog, cat, rat, rabbit, and man has also been investigated.

The subject[1] will be discussed under the following heads:

Section I.—*NORMAL CONDITIONS.*

1. The pulmonary pleura, as regards its endothelium, its matrix, and its lymphatics.

2. The lung proper, as regards its lymphatics and those of the bronchi.

Section II.—*PATHOLOGICAL CONDITIONS.*

1. Changes of the pulmonary pleura in chronic diseases of the lung.

2. The relation of the lymphatics of the lung to the process of artificial tuberculosis in guinea-pigs.

3. Relation of this latter disease to acute miliary tuberculosis in man.

I have at the outset to render my best thanks to the Government Grant Committee of the Royal Society for having again provided the means for the execution of the plates.

[1] A summary of the results of this inquiry had been published in the 'Proceedings of the Royal Society of London,' January 1874.

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Section I.—*THE NORMAL CONDITIONS.*

CHAPTER I.

THE ENDOTHELIUM OF THE PULMONARY PLEURA.

The pulmonary pleura is, like the costal pleura and other serous membranes, covered with a single layer of endothelial cells. There exists, however, a marked difference in morphological characters between the endothelium of the pulmonary pleura and that of other serous membranes. If we take, for instance, the endothelium covering the costal pleura, we find it composed of ordinary flattened nucleated cells, the shape of which is generally that of polygonal placoids. In the normal condition it is always found as such; it is only in pathological processes, especially in chronic inflammations, that we find changes of a certain kind, which will be mentioned in the Second Section, and which may be referred to here by anticipation. In that membrane the endothelial cells surrounding the stomata, first described by Dybkovski,[1] become germinative, *i.e.* they become polyhedral, even shortly columnar, and distinctly granular; while their nucleus shows a constriction or is actually divided into two. Such endothelial cells present, when viewed from the surface in the fresh condition, more the aspect of epithelium. These changes have been

[1] See Notes at end of book.

fully described in the First Part of this work. Now, it is only in the inspiratory condition that the endothelial cells covering the pulmonary pleura are flattened like other endothelial cells; they are quite different during expiration. During inspiration the endothelium of the pleura has to cover a much greater area than during expiration; the lung occupying, in the latter case, a much smaller volume, and consequently also presenting a much smaller external surface than in the condition of inspiration. It is, therefore, a matter of absolute necessity that all those parts that are in a permanent connection with the surface of the lung as a whole, should undergo corresponding changes in the conditions of in- and expiration.

What are the changes that the endothelium of the pulmonary pleura undergoes? To study them I proceed in this manner. The lungs of a freshly killed guinea-pig are moderately distended by injecting air into them through the trachea, and, while kept in that condition by placing a ligature round the root of the trachea, they are dipped into a weak solution of nitrate of silver ($\frac{1}{8}$ to $\frac{1}{2}$ per cent.) and allowed to remain there for a few minutes, after which they are washed in distilled water for a short time, and then hardened in spirit. In this manner horizontal sections can be obtained from the surface, which, after being washed in water, are mounted in glycerine and then subjected to microscopical examination. The surface is then seen to be covered with the well-known network of dark lines (silver lines), which, as is now generally admitted, correspond to the intercellular cement-substance of the endothelium. Here and there the substance of the individual endothelial cells has become conspicuous by the presence of brownish granules, and likewise a clear nucleus of a circular shape, situated excentrically, may be distinguished in many of them. The nuclei may be brought out very prominently by placing the sections, before mounting them, in a weak solution of hæmatoxylin,* to which a few drops of spirit have been previously added. When viewed in profile, as may be done in folds which present themselves here and there in the section, the general surface is seen to be not quite smooth, but slightly notched

* For the preparation of the solution of hæmatoxylin, see the 'Quarterly Journal of Microscopical Science,' October 1873.

between each endothelial cell. This is owing to the fact that the endothelial cells are thicker in the centre than at the point where they are in contact with one another. These notches, as seen in profile, evidently correspond to small grooves between the adjacent endothelial cells; they are the less distinct the more smooth the surface of the endothelium is, or the more the lung has been distended. Owing to the presence of such grooves between contiguous endothelial cells, I have obtained very neat specimens from lungs which, having been injected with Brücke's soluble Berlin blue through the pulmonary artery, had been smeared on their surface with Berlin blue that escaped from the veins or that accumulated on the bottom of the plate on which the lungs had lain during the injection. Horizontal sections, made from the surface of the hardened lung and stained in carmine or hæmatoxylin solution, showed, when examined under the microscope, the endothelium of the pleura in a very striking manner; viz. the outlines of the individual endothelial cells were stained deep blue, owing to Berlin blue having been precipitated in the grooves between the contiguous endothelial cells as above mentioned; the substance of the cells had a faintly stained and distinctly granular appearance, whereas the nucleus came out very prominently as a circular body of a deep pink (carmine) or purple colour (hæmatoxylin).

Different from this is the appearance of the endothelium if the lungs have not been distended. If the lung of a freshly killed guinea-pig be stained in nitrate of silver without having been previously distended, and horizontal sections, comprising the pleura, be examined, the endothelium is found to differ from that of the distended lung in the following respects: (1) The substance of the individual endothelial cells is distinctly granular, whereas in the former case it is pale and transparent, like that of ordinary endothelial cells after silver staining, and (2) the endothelial cells are no more flattened plates, but are polyhedral or even columnar. (3) A third, not so very constant difference, is that the nucleus of the endothelial cells has more a spherical shape, whereas that of the endothelial cells of the pleura pulmonum in the distended lung is generally circular, when viewed from the surface, and appears

oblong when seen sideways; so that it may be said that the nucleus is flattened in a direction parallel to the surface. I said before the endothelial cells are almost columnar in shape; to this it must be added that the tops of the individual endothelial cells are rounded; that is to say, they are cemented together only in their deeper parts, whereas their more superficial parts are separated from each other by deep gaps (compare D in Fig. 1). Owing to this fact the appearance will be different when the superficial or the deeper parts of the endothelial cells are brought into focus; for in the former case the endothelial cells appear as spherical bodies, separated from each other by broad furrows, in the latter case they appear like a continuous mosaic of cells, separated by thin intercellular lines (compare C and B in Fig. 1). (4) Besides the changes above mentioned it will be found that the endothelium of the pulmonary pleura of the collapsed lung stains more readily and more deeply with nitrate of silver than that of the distended lung. It will thus appear that we have the same differences between the endothelium of the pulmonary pleura of the collapsed lung and that of the costal pleura, as between the upper surface of the ovary and the surrounding peritoneum, as described by Waldeyer in his work on the ovary and ovum. Just as on the ovary, so also on the pulmonary pleura of the collapsed lung the covering layer of cells gives one more the impression of an epithelium than of an endothelium. The difference between the endothelium of the pleura of the distended lung and that of the collapsed lung is, however, only striking in guinea-pigs, in other animals (dog, cat, rat, and rabbit) it is distinct, but not so remarkable. The same is the case in man. One finds a marked difference, for instance, between the endothelium of the pleura pulmonum of a human fœtus whose lungs have not yet breathed and that of a newborn child whose lungs are distended by air; in the former case the endothelial cells are small and polyhedral, distinctly granular, and staining readily in nitrate of silver, whereas in the latter case they are flattened transparent plates, just like ordinary endothelial cells. The reason why the lung of guinea-pigs shows the difference with regard to the endothelium of the pleura in the distended and the collapsed lung so exquisitely well, is, I suppose, to be sought in the fact, that the lung of guinea-pigs

collapses on its removal unrelatively more than that of other animals; or, more correctly speaking, it contracts much more than in other animals. This circumstance, again, can easily be accounted for, as we shall see hereafter that in the lung of the guinea-pig the pleura possesses a special muscular coat.

There now falls to be considered, next in order, the question, whether there exist stomata among the endothelial cells of the pulmonary pleura, just in the same manner as they have been demonstrated to exist in the endothelium of the costal pleura. This question, however, we must leave until we have first described the structure of the pleura pulmonis and its lymphatic vessels.

CHAPTER II.

THE MATRIX OF THE PULMONARY PLEURA.

The matrix of the pulmonary pleura is, in its structure, very similar to that of other serous membranes, *i.e.* a connective tissue membrane containing elastic fibres and cellular elements; but it is in so far different from other serous membranes, that it is extremely delicate and thin. In horizontal sections of a fresh lung the pleura appears to be composed of very delicate bundles of fine connective-tissue fibres; after the addition of acetic acid fine elastic fibres may be also recognised. These latter vary in abundance in different places and in different animals. In the lung of rabbit, cat, and dog, they are easily to be distinguished as fine networks of elastic fibres, whereas in the lung of guinea-pig they are much more rarely seen. The connective-tissue matrix is, as has been already stated, composed of bundles of delicate fibres. The best object for examining these is the lung of the newborn child and of the guinea-pig. The latter is especially suitable if the animal suffers from slight chronic pleuritis (associated with chronic inflammatory processes of the lung itself), for then the pulmonary pleura becomes partially thickened, and presents a very favourable object of study. In a horizontal section of such a lung, that has been hardened in spirit, after staining it with hæmatoxylin, the pulmonary pleura is seen to be a thin membrane composed of bundles of fine connective-tissue fibres. These bundles cross each other, or run for some distance even parallel; in any case there are left spaces between the bundles, or, more correctly speaking, between groups of bundles. The size of each of these spaces depends naturally on the extent of the separation of the bundles; and their shape is likewise entirely dependent on the arrangement of the latter.

I must refer the reader to Fig. 4. It may be seen in this figure that some of the spaces (probably all of them) are provided with canals, by means of which they communicate with each other. These interfascicular spaces contain each a flattened nucleated cell—a connective-tissue corpuscle. We shall return to these points again with reference to the general arrangement of connective-tissue bundles and connective-tissue corpuscles when we come to deal with the connective tissue surrounding the larger branches of the pulmonary artery; at present I will be content with mentioning that these interfascicular spaces, containing the flattened connective-tissue corpuscles, correspond to the lymph-canalicular system of other serous membranes as mentioned in the First Part of this work.

The pulmonary pleura is in intimate connection with the septa that separate groups of the superficial alveoli of the lung; it lies closely attached to the upper or external surface of the most superficial alveoli. In guinea-pigs the pleura possesses an element additional to those enumerated above, which stands in an important and intimate relation to the lung in pathological as well as in physiological respects. This additional element consists of bundles of unstriped muscle-fibres. If thin horizontal sections are made of a normal lung, hardened in spirit, and these sections after being stained with hæmatoxylin are examined under the microscope, there are seen beneath the endothelium, covering the free surface, slender bundles of unstriped muscle-fibres, arranged so as to form a network with long rhombic meshes. I was acquainted with all the facts relating to these bundles of unstriped muscle-fibres, from the study of horizontal and vertical sections through the superficial parts of the lung, before I used hæmatoxylin as a staining fluid; but when I used this latter reagent I soon became aware of its great superiority to carmine, and I found that I might have been saved a great deal of time and trouble had I used it earlier. For hæmatoxylin brings out these bundles of unstriped muscle-fibres very conspicuously indeed, the substance of the individual fibres, although but faintly coloured, being very well defined from the general matrix, and their nuclei being deeply and prominently stained. Examining a thin bundle of these fibres under a moderately high power, one soon recognises that

the substance of each spindle-shaped muscle-fibre is composed of minute longitudinal fibrils, thus giving to the whole fibre the appearance of fine longitudinal striation—an appearance which, as is known to histologists (*see* Arnold, in Stricker's 'Handbook'), is found on unstriped muscle-fibres in general. Fig. 3 gives an exact representation of the unstriped muscle-fibres of those pleural muscle-bundles. I said before that this network of delicate bundles or bands of unstriped muscle forms an additional and unique element in the pleura pulmonis of guinea-pigs. I must, however, add that I found also in the pleura of dog and cat isolated spindle-shaped cells with the characteristic staff-shaped nucleus of unstriped muscle-fibres, as well as small bundles of the same. In the pleura of guinea-pigs the network of muscular bundles, as described above and represented in B of Fig. 2, forms a distinct coat, which is, as regards position, subserous, *i.e.* it is placed beneath the proper connective-tissue matrix of the pleura.

Just as there is a difference between the endothelium of the free surface in the distended lung and in the collapsed lung, so there is also a difference to be noticed between the arrangement of the bundles of the plural muscular coat in the condition of ex- and inspiration. It is a matter of obvious necessity that the bundles of the muscular coat in question should be nearer together—that is to say, that the meshes between them should be narrower in the state of expiration than in that of inspiration. In the latter condition the bundles separate from each other widely, according to the greater expansion of the lung, or in other words according to the extent of surface over which they are distributed. Actual observation confirms this fully, for, in horizontal sections taken from the surface of a lung that had been hardened in the expanded condition, the bundles of the pleural muscular coat are seen to be thin and so far apart from each other that there are left between them broad rhombic meshes; whereas, in similar sections of a collapsed lung, the bundles are seen to be thicker, the muscular fibres shorter, and the meshes between the bundles narrowed and elongated to such an extent that in some places the bundles seem rather to form a continuous membrane. From what has been said just now it is no doubt correct to assume that the

muscular bundles contract and extend simultaneously with the lung as a whole. That the pleural muscular coat acts consentaneously with the respiratory movement is rendered probable also by other circumstances. Firstly, the muscular bundles have in general a radiating direction from the apex towards the basis of the lung; secondly, if we examine this muscular coat with reference to its distribution over the different parts of the surface of the lung, we find the remarkable fact that it is developed best on those parts that participate prominently in the respiratory movement, whereas the muscular bundles are thin and scarce, or even wanting altogether on those parts that make only slight excursions during respiration. That is to say, they are to be found most abundant on the external surface, or that directed towards the anterior wall of the chest, and on the internal surface, or that directed towards the mediastinum; on the posterior surface the bundles are scanty, and become more so the nearer to the vertebral column.

The pleural muscular coat is, however, not only of great importance for the respiratory movement of the lung, but it plays also an important part with regard to the lymphatic system of the organ. In the next chapter we shall see that the lymphatic vessels that are distributed on the surface of the lung, and that run through the ligaments of the lung towards the bronchial lymphatic glands, are in communication with the meshes of the pleural muscular coat; and further, that these are again in communication with the free surface, *i.e.* with the pleural cavity. Hence it will be clear that the action of the pleural muscular coat stands necessarily in a direct relation to the lymphatic absorption from the pleural cavity. In consequence of the muscular bundles during inspiration separating widely from each other, and the meshes between them becoming enlarged, it happens that the communication openings between the latter and the free surface are also dilated. While doing this the meshes between the muscular bundles evidently will acquire a pumping action, and be enabled to fill themselves from the pleural cavity. During expiration, on the other hand, while the meshes themselves as well as their communications with the pleural cavity collapse, or rather become compressed, the contents of the former will be pressed into

the lymphatic vessels of the surface of the lung, mentioned above. These relations justify our saying that the pleural muscular coat acts like a pump with reference to lymphatic absorption. In the First Part of this work we have had occasion to mention a similar fact with regard to the lymphatic absorption through the diaphragm from the peritoneal cavity. The action of the pleural muscular coat as a pump will hardly be of any marked effect under normal conditions, as there is so very little to be absorbed from the pleural cavity in its healthy state; but under pathological conditions it will have an effect that cannot be under-estimated, for then the pleural muscular coat may materially assist the absorption of the morbid products contained in the pleural cavity.

CHAPTER III.

THE LYMPHATIC SYSTEM OF THE PULMONARY PLEURA.

The lymphatic vessels of the pulmonary pleura have been studied more recently by Wywodzoff[2] and Sikorsky.[3] According to Wywodzoff the superficial lymphatics, *i.e.* those of the surface of the lung, are placed, in the case of the dog and horse, beneath the proper pleural membrane in the grooves between the lobules, where they form a network. The rootlets of these vessels lie in the septa of the alveoli. The efferent branches of this network communicate with deep lymphatic vessels, but for the most part they run separately towards the root of the lung. According to Sikorsky, the superficial lymphatics of the lung of cats and dogs take their origin from the subpleural alveoli. Their trunks, at first anastomosing with one another, enter the pleura itself and find their way through the ligaments that unite the different lobes, and finally reach the root of the lung.

I have studied these lymphatics in the pleura of the lung of dogs, cats, rabbits, guinea-pigs, and young children. They are best developed and easiest to demonstrate in the lung of dogs and young children. In these instances they may be followed under a lens even in the fresh lung. They appear as clear transparent tubes with a well-defined wall, forming a network, many branches of which correspond to the grooves between the superficial lobules of the lung. The larger branches are very conspicuous by their wavy course, and by their valves as recognised by corresponding constrictions. The lymphatics of the pleura of dogs, as well as those of young children, may be easily injected with a two per cent. solution of Brücke's Berlin blue. To effect this the fresh lung is moderately distended by injecting air into the trunk of the bronchus, and is kept so by

placing a ligature round the former. By means of a Pravaz syringe or a simple glass tube drawn out into a fine canula and bent at a right angle near its point, the Berlin blue is injected, after piercing one of the large lymphatic trunks with the fine canula of the Pravaz syringe or with the fine glass cannula. If the latter is used it is filled with the fluid after having been connected with an india-rubber tube. The injection, *i.e.* the discharge of the fluid, is then effected by the mouth of the operator or with a syringe. Although as a rule the whole network of lymphatics does not become injected by the latter mode, still some portions of it will become well filled. In the same manner nitrate of silver solution may be injected. I have seen once the network of pleural lymphatics beautifully distended with air in a dog that had been kept for more than half an hour under vigorous artificial respiration. In this case most probably some alveoli had been ruptured, and air had escaped into the interalveolar lymphatics that lead into the lymphatic trunks of the pleura. I have found these lymphatics very marked in the fresh lung of children that died in consequence of acute miliary tuberculosis; in many places they could be distinguished as more or less transparent tubes, which, as the microscopical examination proved, were filled with lymph and contained also in some parts lymphoid cells. In some instances I have seen them also in the fresh lung of guinea-pigs that died of chronic pyæmia, brought on by injecting putrid pus into the pleural cavity. The lymphatics were discernible as opaque streaks, owing to their being filled with lymph-corpuscles.

To inject the pleural lymphatics of the lung of guinea-pigs in the same manner as those of dogs is a very difficult task. I have, however, succeeded in some instances in injecting the pleural lymphatics as well as those of the lung proper of guinea-pigs, by injecting Brücke's Berlin blue into the pulmonary artery under so high a pressure that in many places the alveoli became ruptured. (The same may be effected by compressing the pulmonary veins for some time, and by ligaturing the bronchial trunk after the alveoli had been ruptured at certain points.) The rupture of alveoli can, of course, be recognised at once on simple inspection. In the case that is now referred to, the injecting fluid did not only escape into the air-passages,

but filled also the lymphatics of some portions of the lung substance. The lymphaties of the pleura were discernible under a lens as a network of tubes filled with the injection material. From injected blood-vessels this network could be distinguished with great ease by observing its course, its distribution, and the nearly equal diameter of its branches.

Further, the constrictions of the branches which, as we know, correspond to valves, served to distinguish them. Besides, the microscopical examination of horizontal sections made it quite clear that the network was a network of lymphatic vessels.

With regard to the structure of these lymphatic vessels there is very little to be said. Their wall is composed of a single layer of elongated endothelial plates, just like that of other lymphatics. Their distribution has been already mentioned, and it remains only to add that some of the branches are provided with lateral blind saccular dilatations. In examining a horizontal section showing the lymphatics of the pleura, one must be very careful in determining the existence of these blind endings; for a trunk may often appear to end abruptly, which, on examining it with a higher power, can be seen to dip down in a vertical direction or to be continuous with a narrow canal that runs in the deeper parts of the lung, *i.e.* between the alveoli. There exist, however, true blind endings which, even on the closest examination, are seen to be in no connection with lymphatics coming from the depth of the lung. With regard to the mode of distribution of pleural lymphatics, I refer the reader to Fig. 6.

As has been correctly observed by both Wywodzoff and Sikorsky the pleural lymphatics discharge themselves into trunks that run in the ligamenta pulmonis towards the bronchial glands into which they enter.

It has been stated already that there are branches springing from the deeper parts of the lung and entering finally the network of the lymphatics of the pleura. These branches are somewhat different from the branches of the general network. First of all they are decidedly narrower, then they have no valves, and thirdly their endothelial wall, when stained with nitrate of silver, is more like that of lymphatic capillaries than of lymphatic trunks, the endothelium of

the former being shorter and more rhombic than that of the latter. (Compare the First Part of this work.) The branches just now under consideration are of two kinds: (1) branches that originate in the tissue forming the septa of the alveoli of the superficial parts of the lung; (2) branches that form the anastomosis between the lymphatics of the pleural network and those of the lung proper, which, as will be shown fully afterwards, accompany the branches of the pulmonary blood-vessels. These anastomosing branches have been already recognised by Wywodzoff; Sikorsky does not seem to have seen these vessels.

The superficial lymphatics of the lung are situated beneath the proper pleural membrane, and it is therefore more correct to call them *subpleural lymphatics*. In addition to these there exist in the pleura of the lung of guinea-pigs spaces which, being lined by a distinct layer of endothelium, represent lymphatic lacunæ or lymphatic spaces. These are the spaces that have been mentioned above as being enclosed between the bundles of the pleural muscular coat. From observations made on lungs of guinea-pigs suffering from chronic pyæmia (induced by the injection of putrid pus into the pleural cavity), or from artificial tuberculosis (the lymphatics in these cases having been injected with Berlin blue), and from the examination of lungs of guinea-pigs suffering also from artificial tuberculosis (in which cases the surface of the moderately distended lung had been stained with nitrate of silver after pencilling off the endothelium of the pulmonary pleura), I have collected sufficient proof to assert that the intermuscular lymph-spaces are in direct communication with the subpleural network of lymphatics.

There remains now to be discussed another very important point, viz. the question whether a free communication exists between the pleural cavity and the lymphatics that we have been describing hitherto; that is to say, whether there exist stomata on the surface of the pulmonary pleura. Before entering on this question I will avail myself of the opportunity to bring before the reader the question of stomata of the serous membranes in general once more, especially as their existence has been doubted by some recent observers. As I have pointed out in the First Part of this work (see I. Serous

Membranes, p. 49 *et seq.*), Recklinghausen[4] was the first to furnish the experimental proof of the existence of stomata on the peritoneal surface of the diaphragm; Ludwig and Schweigger-Seidel[5] made this probable also in histological respect, and I have established the complete histological proof for those stomata which I regarded as the external openings of perpendicular lymphatic canals. This I have shown to be the case, not only for the central tendon of the diaphragm, but also for the omentum and peritoneum; the conclusion being arrived at from the examination of those membranes in the normal and pathological condition. Previous to this Dybkovski[6] has proved the existence of stomata most satisfactorily on the costal pleura, not only by very striking experiments, but also by microscopical examination. I have farther pointed out, in the First Part of this work, that the stomata of the septum cisternæ lymphaticæ magnæ of frogs, first described by Dogiel and Schweigger-Seidel,[7] represent the openings of perpendicular lymph-canals lined by a special layer of endothelial cells generally of a germinating character. (See Fig. 3 in Part I.) Differing from these observations, Bizzozero[8] denies the existence of stomata on the human peritoneum, as he has not succeeded in demonstrating them on this membrane after hardening it in spirit and after preparing off the most superficial layer from the general matrix. According to this author the subendothelial layer is a complete membrane, and it does not possess any interruptions of its continuity that may correspond to stomata. To these observations I will only add, that I am inclined to think it improbable that stomata could be demonstrated in a serous membrane after hardening it. I will go a little farther than that; I venture to say that it is out of the question to demonstrate even lymphatic vessels in the omentum after hardening it in spirit, although I have demonstrated them in this membrane both in normal and in pathological conditions, in the fresh state as well as after staining it with nitrate of silver. Ranvier,[9] who examined the stomata of the mesentery of the frog, arrived at conclusions with regard to their structure which do not correspond altogether with those stated by Dogiel and Schweigger-Seidel for the stomata of the septum cisternæ, or with those put forward by myself for the latter and for the stomata of the mesentery. According to

Ranvier the stomata are as a rule not free openings, but are in the normal condition plugged up by a granular protoplasmic cell. This I regard as incorrect. The protoplasmic mass that Ranvier finds occupying the stoma is probably one or more of those endothelial cells belonging to the special lining of the stomatous canal (such as I have figured and described over and over again), which endothelial cells have become detached from the wall of the stomatous canal in consequence of the preparation having been stretched excessively. In this opinion I am confirmed, not only by my own experience of stretched and unstretched membranes, but by Ranvier's drawings themselves; for the appearance of the thick and sharply defined wall with which his stomata are surrounded is clearly a result of the membrane having been stretched too much. In carefully prepared specimens the appearance is not met with. Just the opposite is to be found in the description given by Tourneux [10] of the stomata of the cisterna lymphatica magna. This author maintains that the so-called stomata of the septum cisternæ are merely pits in that membrane, which are lined by special granular cells; and he thinks they resemble secreting glands lined by epithelium. This assertion can be accounted for by bearing in mind that in a shrunken septum, where the stomata are collapsed, they certainly have the appearance of pits lined by granular cells; these latter are the granular cells that have been described by me as forming the special lining of the stomatous canals. That this view of Tourneux is erroneous can be shown in a well-prepared septum, where the stomatous canals, penetrating the septum and lined by a special layer of granular endothelial cells, may be easily recognised, both on the peritoneal and on the cisternal surface. (See Fig. 3, Part I. of this work.) And, in addition to this, it can be easily shown that formed particles may penetrate freely from the peritoneal cavity into the cisterna, the septum itself being uninjured. Facts bearing out this point have been already mentioned by Dogiel and Schweigger-Seidel; in addition to these I will mention an observation that may be repeated very easily. A male frog is killed, its peritoneal cavity opened and the septum cisternæ exposed by pushing the intestine to the opposite side; if on the peritoneal surface of the septum blood is allowed to drop from a capillary glass tube, it is seen

after some time to be contained in the cisterna. The septum is cut out and prepared for microscopical examination after staining it with solution of nitrate of silver. Many stomatous canals are then seen to contain blood corpuscles, which may be easily traced through those canals from one surface of the membrane to the other. In male frogs this experiment succeeds much better than in female, for in the former the endothelial cells lining the stomatous canals do not possess cilia, whereas many of them in female frogs are ciliated, especially during the winter months. (See p. 52, Part I. of this work.)

With regard to the lymphatic vessels of the pulmonary pleura, I have very little doubt that they are in free communication with the pleural cavity, *i.e.* that there exist stomata amongst the endothelium of the free surface. The facts that lead me to this assertion are these :—*a.* In rabbits and rats that died a few days after the injection of putrid pus into their pleural cavity, I have seen, attached to the surface of the pulmonary pleura, cords of coagulated fibrin (the pleural cavity containing an abundant fibrinous exudation, and numerous pus corpuscles, as well as in some places false membranes of lymph), which cords could be traced on microscopical examination through canals from the surface into lymphatic vessels of the pleura. *b.* In rabbits and guinea-pigs that were suffering from chronic pyæmia in consequence of injecting putrid pus into their pleural cavity, I have been able to find germination of the endothelial cells over certain spots of the surface (see Fig. 1). It happened either that in the centre of these groups of germinating endothelial cells a distinct opening could be detected, or that lymphoid cells could be traced in a continuous row from the surface through those openings into the plural lymphatics. Similar observations I have described and illustrated in the first part with reference to the serous membranes. *c.* The same relations could be shown to exist on the pulmonary pleura of guinea-pigs that suffered from artificial tuberculosis. *d.* But also in healthy guinea-pigs I have seen the free communication between the pleural cavity and the intermuscular lymphatic spaces referred to above. In a lung moderately distended

and stained with silver, these intermuscular spaces were seen in many places to be covered only by a very thin film on which the surface endothelium rested. Distinct holes could be detected between the surface endothelium just above the intermuscular spaces, and these holes led through short canals into the spaces themselves. I have been much more successful in the examination of the lungs of guinea-pigs suffering from artificial tuberculosis; in these cases horizontal sections of a lung that had been moderately distended and then stained with nitrate of silver, showed the stomata of the surface leading into the intermuscular lymph-spaces quite satisfactorily. Troisier[1] has recently published a paper on pulmonary lymphangitis, in which he also maintains the existence of stomata on the surface of the lung. (The existence of these stomata was first pointed out in my preliminary notice in the 'Proceedings of the Royal Society,' January 1874.)

Having described all that refers to the lymphatics of the pulmonary pleura, we are able now to give a brief sketch of the process of absorption by these lymphatics as it necessarily follows from their anatomical relations. It is quite clear that the respiratory movement of the lung is a factor that plays the most important part in this process. When the lung expands, as during inspiration, it will necessarily have the effect that the stomata of the surface are opened widely, and that the intermuscular lymph-spaces of the lung of the guinea-pig, as well as the proper lymphatic vessels of the pulmonary pleura, become distended. Under these conditions the lymphatic system will become filled with material that happens to be in the pleural cavity, and that is able to pass through the stomata. During expiration, on the other hand, the stomata as well as the lymphatic spaces and proper lymphatic vessels will become compressed, so that their contents will be discharged into the efferent trunks. In guinea-pigs the action of the respiratory movement of the lung is greatly supported by the pleural muscular coat. Likewise it is clear that during inspiration those lymphatic branches also will become distended that originate in the septa of the superficial alveoli of the lung, and discharge themselves, as has been mentioned, into the network of the sub-pleural lymphatics. During expiration, again, they will become compressed. Further branches, that have been described

above as forming the anastomosis between the lymphatics of the pleura and the lymphatic vessels, to be afterwards referred to, belonging to the lung proper, and accompanying the branches of the pulmonary blood-vessels, represent, so to speak, the safety-valves for the sub-pleural lymphatics during expiration.

CHAPTER IV.

THE LYMPHATIC SYSTEM OF THE BRONCHI.

According to F. E. Schulze,[12] numerous lymphatics take their origin in the internal layer of the bronchi, and having passed through the external connective-tissue adventitia, run towards the root of the lung, where they enter the bronchial glands. Sikorsky examined the lymphatics of the bronchi of cats and dogs, into whose air-passages a watery solution of carminate of ammonia had been introduced during life. On microscopical examination, the carmine has been found to be present only in the lymphatic system, and hence it was possible to trace the lymphatic vessels up to their minutest branches. Thus he found that there exist, between the columnar epithelial cells of the bronchial mucous membrane, peculiar structures, on superficial aspect resembling columnar epithelial cells, which take up very readily the carmine, whereas the ordinary epithelial cells do not become stained by it. These interepithelial structures are in connection with fine canals, which run perpendicularly into the depth of the bronchial mucous membrane. Partly in the proper mucosa, but chiefly in the sub-mucosa, they form a dense network of anastomosing canals, from which the lymphatic trunks take their origin. These latter are situated in the sub-mucosa, and accompany the bronchi towards the root of the lung.

We will first examine the large lymphatic vessels of the bronchi. In the large, as well as in the middle-sized bronchi, numerous lymphatic vessels are found in the connective tissue adventitia. Here they form a network, the individual vessels having for the most part a course parallel to the long axis of the bronchus. With these lymphatics, other vessels are seen to anastomose, which latter emerge

from that part of the bronchial wall that is nearest to the circular muscular coat, and represents the proper sub-mucous tissue. In small bronchi which are devoid of cartilage, and the wall of which consists merely of epithelium, a thin mucous layer, a circular muscular coat, and a connective-tissue adventitia, the network of lymphatic vessels in the latter is also very distinct. It will be noticed as an important fact that most of the lymphatics are distributed in that portion of the wall of the bronchus which is next to the branch of the pulmonary artery, and which forms a part of what is also described as the bronchial adventitia. For the sake of greater clearness we propose to call these lymphatics that are situated in the adventitia *the peribronchial lymphatics*. The network of peribronchial lymphatics is composed of trunks that chiefly belong to the bronchus itself, *i.e.* they are supplied by the bronchial wall itself. Some of these vessels, however, represent merely the anastomosis of the former with the lymphatic vessels that run along with the larger blood-vessels. The latter we shall become acquainted with hereafter, as *perivascular lymphatic vessels*. I will refer the reader to fig. 18, in which the peribronchial lymphatics are seen to anastomose with perivascular ones.

If we examine the smaller bronchi of the lung of guinea-pigs, especially of those that suffer from artificial tuberculosis, we meet with very marked structures situated in the wall of one of those peribronchial lymphatics that extend between the branch of the pulmonary artery and the contiguous portion of the bronchus. These structures are spherical, oblong, or even cordlike accumulations of adenoid tissue in the wall of a lymphatic, on the side that is looking towards the bronchus. They are met with in various numbers in different parts of the lung, and also of various sizes. Those amongst them that are of a considerable size are provided with a special network of capillary blood-vessels, as is represented in figs. 8 and 18. In this respect, and in their being composed of a reticulum of fine fibres with lymphoid corpuscles in its meshes, they perfectly resemble lymphatic follicles. They have been described by Burdon Sanderson [13] in this way:—'Masses of cytogenic tissue of irregular form are always to be found in the neighbourhood of the

bronchi (of the lung of guinea-pig). Those which are in relation with the smaller branches lie in the loose common connective-tissue, by which these tubes, as well as the blood-vessels are separated from the air-cells; while those which lie near bronchi of sufficient size to be possessed of cartilages, are found to lie in a corresponding position outside of the fibrous layer in which the cartilages are embedded. In every instance I have found the adenoid masses occupying a position between the air-tube and the nearest artery, with the outside of the adventitia of which the surface of the mass is usually, if not always, found in contact.' It is further to be noticed, that in injected lungs 'the masses were found to be vascular, minute capillaries, not only ramifying on their surface, but penetrating into their interior.' With regard to the relation of these masses to the lymphatics, B. Sanderson writes thus: 'I am unable to state anything from my own observations as to the relation of these bodies to the lymphatic system; but inasmuch as they lie in the course of the absorbent vessels, I have no doubt that they are in direct relation with the lymph.'

As has been stated above, they bear a definite relation to lymphatic vessels. In the normal as well as in the tuberculous lung of guinea-pigs I have satisfied myself as to the development and continuous growth of these lymphatic follicles in the wall of a peribronchial lymphatic, situated between the branch of the pulmonary artery and the bronchus itself. The wall of such a lymphathic vessel, composed only of a single layer of endothelial plates, becomes thickened so as to present the appearance of a cell-reticulum, which, as it grows, assumes more and more the character of lymphatic or adenoid tissue, and which is observed to be in direct connection with the endothelial wall of the lymphatic. During its growth, the lymph-follicle, which chiefly extends toward the inner stratum of the bronchial wall, bulges in that portion of the wall of the lymphatic to which it belongs; so that, after the follicle has reached a certain size, its outer surface appears to be surrounded by a semilunar lymph-space or sinus, lined by endothelium (compare figs. 5 and 8). But in fact, this semilunar sinus owes its shape only to the bulging in of one of its walls by the growth of the lymphatic

follicle. Thus we have here precisely the same relations as described by me with regard to the serous membranes, *i.e.* the development of lymphatic follicles in the wall of a lymphatic vessel outside its lumen. These follicles I have called perilymphangeal follicles, and the same name may be applied to those of the bronchial walls. In small bronchi, which are devoid of cartilage, lymph-follicles are to be met with, extending not only close up to the muscular coat, but also protruding through this latter into the proper mucosa, *i.e.* into the layer between the epithelium and the muscularis. In the latter case also, the lymph-sinus surrounding the follicle is seen to extend into the muscularis. These lymphatic follicles in the bronchial walls are therefore in every respect analogous to the lymph-follicles found in other mucous membranes, *e.g.* in the tonsils and in the intestine, as well as in the cortical part of true lymphatic glands (*viz.* mesenteric glands, inguinal glands, &c.).

I have met with lymphatic follicles in the wall of bronchi not only in the lung of guinea-pigs, but also in that of rabbits. There seems to be, however, a slight difference in the case of those two animals. In the lung of rabbits the follicles are less numerous, and are of a less dense structure than in that of guinea-pigs; while in the latter the follicles have a complete resemblance, as regards structure, to those commonly found in other parts, appearing, in preparations not shaken out, to be composed merely of a dense assemblage of nucleated lymphoid cells; in the lung of the rabbit, on the other hand, they seem to be more spongy, showing a reticulum with wider meshes, and with much fewer lymph-corpuscles in them than is the case in ordinary adenoid tissue.

The lymphatic vessels belonging to the bronchial adventitia are, as has been already mentioned, chiefly supplied by rootlets that lie in the internal strata of the bronchial wall. These rootlets are lymphatic branches, which in large bronchi have still distinctly the character of lymphatic tubes, as can be shown in injected preparations. Also in small bronchi there are here and there such short branches met with, emerging from between the muscular coat and taking a somewhat oblique course towards one of the peribronchial lymphatics. As a general rule, however, such lymphatic

tubes are scarce at some distance from the adventitia, the chief mode of arrangement of the rootlets of the lymphatics being here merely that of lymph-spaces. These bear the same relation to the ground-substance as the lymph-canalicular system or the interfascicular lymph-spaces of other connective-tissues; that is to say, there exists a system of communicating spaces in the mucosa, in the muscular coat, and the tissue next to the external surface of the latter, which are merely interfascicular spaces, *i.e.* spaces between the bundles constituting the matrix. The size of these spaces depends entirely on the amount of separation of the contiguous bundles. These interfascicular spaces are, as a rule, much smaller in the proper mucosa than outside the muscular coat, *i.e.* in the adventitia, the bundles of the matrix lying more densely together in the former than in the latter. Moreover, the spaces found in the mucosa are much more like a regular lymph-canalicular system, consisting of lacunæ and anastomosing canals; whereas, in the loose tissue of the adventitia, they resemble more elongated or rhombic spaces, connected only by a few short canals. This difference is, as far as I can see, due to the bundles being arranged in the former place more like a felt, in the latter more like a fenestrated membrane. The interfascicular lymph-spaces are at the same time the spaces in which the connective-tissue corpuscles are found, the latter being, as is now admitted by most histologists, only linings of the bundles bordering the lymph-spaces. As the lymph canalicular system is in open communication with the lymphatic vessels of the bronchial adventitia, it necessarily follows that also the connective-tissue corpuscles are directly continuous with the endothelium forming the wall of the lymphatic vessels. This fact has been fully treated in the First Part of this work. Another question is, whether the flattened connective-tissue corpuscles lining the interfascicular lymph-spaces are branched cells like those of the cornea, or whether they are more of the shape of true endothelial cells, viz. unbranched cell-plates arranged in a continuous row, and held together by an intercellular substance appearing as lines between the cells, just as on the surface of a serous membrane, or on the wall of a lymphatic vessel. In the First Part of this work I have stated, contrary to the assertions of some recent

observers, that in the serous membranes both these forms exist; on the one hand we find places where the interfascicular lymph canal system is made up of lacunæ, anastomosing with each other by canaliculi, and thus resembling the lymph-canalicular system of the cornea, while in other places the lymph-canalicular system is more like a system of large spaces or lacunæ. In the former there lie flattened connective-tissue corpuscles of the same general outline as those of the lymph-canalicular system, being composed, namely, of a cell body and processes anastomosing with each other; the latter, again, are lined by rows of connective-tissue corpuscles perfectly resembling an endothelium. Finally, I have drawn attention to the intermediate and transitional condition of these two kinds of lymph-spaces and their respective cell linings. This relation between the interfascicular lymph-canalicular system and its lining connective-tissue corpuscles I have found to obtain also in the bronchi; that is to say, in the loose tissue of the adventitia the lymph-canalicular system is represented by large interfascicular spaces lined by connective-tissue corpuscles that are perfectly identical with endothelial cells, whereas in the denser mucosa the connective-tissue corpuscles have more the shape of branched cells. In determining the existence of branched cells in those situations, there is a source of fallacy that may be mentioned. It is not uncommon to get, in vertical sections, and more especially if the tissue of the matrix has shrunk, an appearance as if of branched cells, which is really dependent on the section passing through the endothelial membrane. Comparison of horizontal sections will remove the ambiguity in such cases.

Nevertheless, whether the connective-cells lying in the interfascicular lymph-spaces are branched or unbranched, it is quite clear that they are in continuity with the endothelium of lymphatic vessels. What has been asserted hitherto about the interfascicular lymph-canalicular system of the bronchi is in perfect agreement with the description given by me for the serous membranes in the First Part of this work, and also with what I said in my paper on Sheep Pox ('Transactions of the Royal Society of London,' 1874) with regard to the interfascicular lymph-system of the skin. It is also in

agreement in its principal parts with the descriptions given by Axel Key and Retzius,[14] Kyber,[15] Mihalkovics,[16] and others. To the assertions of Kyber we shall have to return by-and-by.

In the experiments of Sikorsky mention has been made of carmine particles penetrating between the epithelial cells of the bronchial mucosa into the lymphatic system of the bronchus. A careful examination of the epithelium of the bronchial mucous membrane proves the existence of peculiar nucleated cells amongst the ordinary epithelial cells. In teased preparations and in sections, especially in horizontal and oblique directions, of the bronchi in dogs, guinea-pigs, and, best of all, in rabbits, I found nucleated cells—apparently branched — which, from their general morphological aspect, and from their mode of staining with staining fluids, are distinctly different from epithelial cells. First of all, in vertical sections they appear distinctly branched; that is to say, they possess a small body containing a small nucleus, and are drawn out into at least two processes, one directed towards the mucosa and one turned in the opposite direction towards the free surface, the cell-body lying for the most part nearer to the proper mucosa than to the free surface. Secondly, these cells are conspicuous by their opacity being greater than that of the surrounding epithelial cells, and by their small nucleus becoming much more deeply stained by hæmatoxylin than the nucleus of an epithelial cell. That process of the cell that penetrates into the mucosa is generally single, but it may be seen to divide; at any rate, it forms a continuity with the connective-tissue cells of the mucosa. The other process penetrates as a well-marked streak between the epithelial cells, and reaches up to the free surface. The appearance is quite different from that of mere intercellular cement substance, and the process may indeed be seen occasionally to give off from one or the other side a branchlet, which, becoming gradually thinner, seems to lose itself in the interepithelial cement substance. That these structures are, therefore, not epithelial cells is proved by their difference of shape, their refractive power, the character of their nucleus, and their mode of staining—in short, by all their morphological characters. They present a very striking appearance in

horizontal sections through the mucosa of a bronchus, as represented in fig. 9, where they are viewed from the surface; the difference between them and the surrounding epithelial cells is very obvious.

It has been just mentioned, that these interepithelial structures are continuous with the subepithelial connective-tissue, and it might be, perhaps, suggested that they are, after all, epithelial cells in connection with connective-tissue corpuscles, similar to those described by Heidenhain, Huxley, Key, Billroth, and others. This view I cannot accept, for the simple reason, that these structures are so strikingly different from epithelial cells in their morphological characters; on the contrary, I must maintain that their connection with connective-tissue corpuscles proves them to be interepithelial connective-tissue cells. The important question now presents itself, what is their physiological value? In the serous membranes I have pointed out a cellular tissue that on the one hand reaches up to the free surface of the serous membrane between the covering endothelium, and on the other hand is in anatomical continuity with the connective-tissue cell-plates of the matrix. These interendothelial cells I have called pseudo-stomatous tissue, for the reason that, while a true stoma is an actual canal leading free from the surface of the serous membrane into a superficial lymphatic vessel, these so-called pseudo-stomatous connective-tissue cells occupy a corresponding system of spaces which, in the natural condition, do not form open communications between the surface and the interfascicular lymph-canal system containing the connective cells of the matrix. Under certain circumstances, indeed, as when distended, they may be converted into free passages between the two. This pseudostomatous tissue is, as I have pointed out in the First Part of this work, of great importance in the normal as well as in the pathological condition; and it is with precisely the same relative structures that we have to do in the bronchial mucous membrane. The reader will already have perceived that the interepithelial connective-tissue cells, previously described, correspond to such pseudo-stomatous tissue, that is, to a tissue forming a connection between the free surface and the connective-tissue cells of the mucosa. This may be expressed also by saying that the spaces in which the pseudo-stomatous cells lie are the

canals of communication between the free surface and the inter-fascicular lymph-spaces, in which lie the connective-tissue cells of the mucosa. We are now enabled to understand how, in the experiments of Sikorsky, pigment or other formed particles may penetrate between the epithelial cells into the lymph-spaces of the bronchial mucous membrane.

I may mention, before concluding this chapter, that Mr. Herbert Watney has found analogous relations with regard to the mucous membrane of the alimentary canal, which, I believe, are of great importance for understanding the normal process of absorption in the intestinal canal.

CHAPTER V.

THE PERIVASCULAR LYMPHATICS OF THE PROPER LUNG-TISSUE.

According to Wywodzoff there exists in the connective-tissue wall of the alveoli of the lung of dogs and horses a system of small anastomosing lymph-canals, the larger of which run in the direction of the elastic fibres and then follow the course of the capillary blood-vessels, at the same time crossing the latter in many places. In the meshes of the capillary blood-vessels they become confluent, so as to form lacunæ. These canals and lacunæ represent the rootlets of the lymphatic vessels of the lung.

Sikorsky found, in his experiments, that there exists in the walls of the alveoli a special network of spaces which consists of canaliculi and lacunæ, the latter being situated at the nodes where the canaliculi anastomose. The lacunæ are of an irregular shape, triangular, rhombic, or stellate, and are always found to be situated in the meshes between the capillary blood-vessels. The canaliculi cross the blood-vessels in all directions. This system of canaliculi and lacunæ form the rootlets from which the lymphatic trunks originate that accompany the larger blood-vessels. These trunks are situated in the adventitia of the arteries and veins, generally a couple of them to each blood-vessel. They enter the root of the lung together with the veins.

In the previous chapter mention has been made of the existence of numerous lymphatics around the large branches of the pulmonary artery. In the connective tissue that surrounds the smaller (large microscopical) branches of the pulmonary artery, lymphatics are discernible as regular tubes, and also as irregular spaces or simple lymphatic cavities. To understand these it is necessary to bear in mind

that the connective-tissue supporting the artery is composed of delicate bundles of fibrillar tissue, which have a loosely fenestrated and wide-meshed arrangement. These meshes correspond naturally to the interfascicular spaces of other loose connective-tissues, and they are lined by the connective-tissue corpuscles that cover the bundles, as if by an endothelium. I refer the reader to Fig. 14. The perivascular lymph-spaces are best seen in lungs of guinea-pigs suffering slightly from artificial tuberculosis, for in these cases they appear dilated and filled with a material which, in hardened specimens, possesses a granular appearance; in this material lymphoid corpuscles are found occasionally imbedded.

Such lymphatic spaces are found in the surrounding connective-tissue both of large and small arteries; in the large arteries, however, there are more of the regular lymphatic tubes and fewer of the lymphatic spaces, while in the small arteries the reverse is the case. But it must be clearly understood that in the small vessels also there are regular lymphatic tubes; only, as a rule, the lymphatics are more commonly represented by a communicating system of simple interfascicular lacunæ. In specimens in which the lymphatics have been injected, it is clearly to be seen that both the true lymphatic tubes and the lymphatic lacunæ form one communicating system, and are therefore in no way different from what we find in lymphatic glands. Precisely the same arrangement has been described by Kyber [17] with regard to the lymphatics around the large branches of the splenic artery, and I will refer the reader to his paper and illustrations.

There is one point with regard to the branches themselves of the pulmonary artery, which may be here mentioned, and which I think has not been noticed hitherto. It is with reference to the muscular coat. In the lung of guinea-pigs the muscular coat of the branches of the pulmonary artery is different from that of other arteries, being in the former not a continuous membrane composed of circular unstriped muscle-fibres, but having in many places the muscular fibres grouped together in distinct bundles separated by connective-tissue in such a manner that the muscular coat is discontinuous, and is wanting from place to place. The bundles are moreover very unequal in diameter. Some branches have at certain places a relatively very

thick muscular coat composed of distinct bundles, while not far from this the bundles are small and widely separated from each other, so that the intima is in direct contact with the adventitia. This relation is best seen in animals suffering from artificial tuberculosis or from chronic pyæmia. Here not only the discontinuity between the muscular bundles, but also the excessive development of some of the bundles, is very marked. (Compare Figs. 14 and 16.)

By the side of the arterial branches are found lymphatic vessels, which have no valves, and whose wall is composed, as seen in silver preparations, of sinuous endothelium, such as is found in capillary lymphatics. With regard to the number of such lymphatics accompanying the smaller arterial branches, there exists great variety. In most places where one has an opportunity of seeing them, they are single; in some, however, they are also found in couples, which may even anastomose with each other by a lateral branch and in still other cases I found instead of true lymphatic tubes a system of lymphatic spaces around the blood-vessel. In both cases the lymphatic is seen at some places to surround the blood-vessel in the manner of an invaginating lymphatic, *i.e.* the blood-vessel appears to be situated with more or less of its circumference inside the lymphatic. Especially where the lymphatic is represented by a system of spaces, the blood-vessel appears in some places to pass right through them. This relation is more commonly found with the branches of the pulmonary vein. With regard to the larger venous branches, there is very little to be said different from what has been already stated for those of the arterial system. Around them there are found, just as around the arteries, true lymphatic vessels as well as lymphatic spaces. But around the smaller branches a true lymphatic vessel is not a common occurrence; in most places only lymphatic spaces are found surrounding the blood-vessel.

It is a matter of some difficulty to demonstrate the perivascular lymphatics of the smaller branches of the pulmonary artery and vein. Ordinary preparations, *i.e.* sections of hardened injected or non-injected lung, show hardly anything of them. The conclusions I have drawn in the foregoing were arrived at from the examination chiefly of lung of guinea-pigs suffering slightly from artificial tubercu-

losis, for in these cases the lymphatics are found to be in many places distended by lymph and therefore discernible. In addition to these, it happened that in a few cases in which I injected the blood-vessels with Berlin blue under a high pressure, also the perivascular lymphatics of some portions of the lung were found to be filled with this fluid. A third kind of examination, that has yielded satisfactory results, consisted in first injecting a very diluted solution of nitrate of silver ($\frac{1}{4}$ to $\frac{1}{8}$ per cent.) under high pressure into the blood-vessels of the guinea-pig's lung, and then freezing it in order to make sections; these were then treated like ordinary silver-stained objects.

The ultimate branches of the pulmonary artery and vein are likewise accompanied by true lymphatic vessels, and it is these vessels that take up the lymphatic rootlets situated in the tissue between the alveoli, *i.e.* in the alveolar septa.

The alveolar septa of the lung of guinea-pigs, which I have chiefly examined with regard to those rootlets, contain besides the well-known system of capillary vessels, also connective-tissue and elastic fibres. The latter are not very numerous; they are chiefly isolated fibres, branching so as to form a network. As a rule, they twine round the capillary blood-vessels. The connective-tissue appears in the form of transparent nucleated cells of the same character as ordinary connective-tissue corpuscles, namely, as flattened cell-plates. These cell-plates are provided with processes, by means of which they form a network. To the connective-tissue cell-plates correspond spaces of the shape of more or less irregular lacunæ; that is to say, the cell-plates line a system of spaces situated between the capillary blood-vessels and analogous to the lymph-canalicular system of other parts. In preparations stained with nitrate of silver (either in the manner above stated, or cut simply from frozen lung and dipped in solution of nitrate of silver, and then treated in the ordinary manner), the lymph-spaces are brought out as a system of irregular lacunæ communicating by fine canals, just as those seen in the cornea after treatment with nitrate of silver. The lymph-canalicular system is seen in such preparations of the lung to be situated in the walls of the alveoli (see figs. 12, 13). In injected preparations, however, the lymph-canalicular system appears, probably owing to distension, to be a network

of rather broad canals which in some places, especially in the nodes of the network, possess lacunar distensions. By staining such preparations with hæmatoxylin, the nuclei of the transparent cell-plates lining this system of lymph-spaces are brought out (see Fig. 19). There cannot be the slightest doubt about this system being in direct communication with the ultimate perivascular lymphatic vessels, and therefore it may be quite correctly regarded as representing the rootlets of the latter.

What has been stated in the foregoing with regard to the rootlets of the perivascular lymphatics holds good also for those branches of the sub-plural lymphatics which, as we have seen in a former chapter, originate in the walls of the superficial alveoli. Precisely the same appearances are demonstrable in the latter, *i.e.* a lymph-canalicular system lined by connective-tissue corpuscles, and in connection with the radicles of the lymphatic vessels. As may have been already noticed, the description given here of the interalveolar lymph-canalicular system corresponds in its principal parts to that given by Wywodzoff and Sikorsky, with the difference, however, that the connective-tissue cell-plates lining this system have been omitted altogether by those observers. There is one other point referring to the interalveolar lymph-canalicular system which may be worth while considering, viz. the appearance of it in silver preparations, as represented in Figs. 12 and 13. A great deal has been recently said for and against the method of demonstrating the lymph-canalicular system by staining the tissue with nitrate of silver, and it is undoubtedly true that in some instances a mistrust in its value is to a certain extent justified. But where the appearances produced by nitrate of silver can be controlled by other methods, as, for instance, in the case of the cornea, by the method of staining it with chloride of gold, or by injection, or by careful examination of sections of hardened tissues, this scepticism is not quite justifiable; and it is still more unjustifiable to abandon the silver method as of no value whatever, as some recent observers have done. One thing certainly may be said, which is, perhaps, not in its favour: it is a method which requires a great deal of attention, otherwise it is apt to mislead by producing very confused appearances.

It remains now to consider the relation of the interalveolar lymph-canalicular system to the alveolar cavities. Sikorsky maintains that the lacunæ of the interalveolar lymph-canalicular system stand in direct communication with the alveolar cavities by means of fine canals, similar to those that are found in the alveolar walls. Buhl,[18] regards the alveolar cavities as lymphatic cavities which are lined by endothelium and stand in free communication with the interalveolar lymphatics. Now, that the alveolar cavities are lined by epithelium, and not by endothelium, *i.e.* by a continuation of the epithelium of the bronchi, and not by the continuation of a subepithelial endothelium, as Debove[19] at first maintained, is a fact well known from embryological studies, which show that in the embryo the bronchi and their terminations (*i.e.* the alveoli) are both lined by epithelium derived from the hypoblast, forming the fore-gut. Secondly, although it may be conceded that pigment-particles penetrate from the alveoli into the lymph-canalicular system, as in the experiments of Sikorsky, or, as is proved by Knauff[20] with regard to carbon particles, that they find their way from the alveoli into the lymphatics of the lung, it does not necessarily follow that the lymph-canalicular system is in free communication with the alveolar cavities. On the contrary, the case of the pseudostomata of the bronchi, as described in the last chapter, furnishes an analogy against this; and, indeed, careful microscopic investigation proves that the very same condition (of pseudostomata) exists also in the walls of the alveoli. The connective-tissue cell-plates that lie in the alveolar septa and line, as we have seen, the interalveolar lymph-canalicular system, are found actually penetrating into the alveolar cavities; they project between the flattened epithelial cells that line the alveolar cavities, in the same manner as has been shown for the bronchi and for the serous membranes. In this way an indirect communication is established between the alveolar cavities and the lymph-canalicular system. These canals may, therefore, be described in this situation also as pseudostomata; and it will, I think, be admitted that under certain conditions these pseudostomatous canals may be distended so that even formed particles may find their way from the alveolar cavities into the lymph-canalicular system of the alveolar walls. In

fact lymphoid cells may migrate, under pathological conditions, from the alveolar cavities into these lymphatics. Fig. 11 shows the relation of the interalveolar connective-tissue cell-plates to the alveolar cavities or their lining epithelium respectively.

If the wall of an alveolus of a silver preparation, as in Fig. 13 B, is viewed from the surface, small circular figures are seen between the lining epithelial cells indicated by the well-known silver lines; from what has been stated just now it is very probable that these small figures correspond to the pseudostomata of Fig. 11.

The lymph-paths of the lung may be now summarized as follows: the radicles of the lymphatic system of the lung are distributed over three different parts: (1) the walls of the alveoli, (2) the walls of the bronchi, and (3) the pulmonary pleura. The first system is represented by irregular lacunæ and anastomosing canals, being the spaces for the branched connective-tissue corpuscles; it gives origin to lymphatic vessels which are provided with a special endothelial wall. According to their position the latter may be regarded, in accordance with the views of previous authors, as superficial and deep lymphatics; the former are situated on the surface of the lung—*subpleural lymphatics*—and form a network, the efferent trunks of which run along the pulmonary ligaments towards the root of the lung; the latter remain in the substance of the lung, and accompany the branches of the pulmonary artery and vein—*perivascular lymphatics*. One of the chief characters of the latter, especially of those situated around the arteries, is their being replaced in some parts by a system of lymphatic spaces, *i.e.* larger or smaller spaces between the connective-tissue fasciculi, and lined by connective-tissue corpuscles, arranged like a true endothelium. Around the large blood-vessels these lymphatic vessels form a network, the efferent trunks of which run towards the root of the lung.

The second system of radicles, viz. that situated in the wall of the bronchi, is represented by irregular lacunæ and anastomosing canals in the mucosa, in the more external parts, *i.e.* in the adventitia by smaller or larger spaces, owing to the different arrangement of the connective-tissue fasciculi; both contain, or, more correctly speaking,

are lined by, the connective-tissue corpuscles, with this difference, that in the former the connective-tissue corpuscles are more like ordinary branched cell-plates, while in the latter they form more a continuous endothelium. The lymphatic vessels originating from these radicles are provided with a special endothelial wall, and form in the adventitia of the bronchi a network—*peribronchial lymphatics*. These are in communication with the larger trunks of the perivascular lymphatics; the efferent vessels of both are identical.

The third system of radicles, viz. those in the pulmonary pleura, are also interfascicular lacunæ communicating with one another by a few canals; each lacuna is lined by a connective-tissue cell-plate. In the guinea-pig's lung there is in addition a system of oblong lymph-spaces formed by the bundles of unstriped muscular tissue—*intermuscular lymph-spaces*. Both discharge themselves into the subpleural lymphatics.

In the lung of guinea-pigs and rabbits the wall of the bronchi contains *lymphatic follicles* in connection with the wall of the peribronchial lymphatic vessels.

The subpleural lymphatic vessels stand in a direct open communication with the pleural cavity by means of *stomata*. The radicles of both the perivascular and peribronchial lymphatics stand in an indirect communication with the alveolar cavities or the surface of the bronchial mucous membrane respectively, by means of *pseudostomata*.

Section II.—*THE PATHOLOGICAL CONDITIONS.*

CHAPTER VI.

THE PLEURA PULMONUM IN ACUTE AND CHRONIC INFLAMMATION.

In the First Part of this work it has been mentioned that the endothelium of the serous membranes is at certain places in a germinating condition, and that this is to a great extent increased in chronic inflammation; and further, it has been stated that similar changes occur also in acute inflammation. Similar inflammatory changes may be observed on the endothelium covering the pulmonary pleura. I have had the opportunity of examining the endothelium of the pulmonary pleura in a good many cases of acute and chronic pleuritis in rats, rabbits, and guinea-pigs. The inflammation was produced by injecting into the pleural cavity septic pus, or peritoneal fluid of dogs or guinea-pigs that had died in consequence of pyæmia. The fluid was introduced into the pleural cavity either by means of a Pravaz syringe, or, as is more preferable, by means of a capillary tube of thick glass; in the latter case, the end which is to be inserted into the pleural cavity is drawn out into a short thin canula with blunt point. To insert this canula or that of a Pravaz syringe I proceed in the following manner:—By a very short incision into the skin next to the sternum in the region of the fourth or fifth intercostal space of the right side, the intercostal muscle can be easily reached; this is then perforated by the point of the canula in an oblique direction, so that its point is directed towards the head of the animal; after the canula has been pushed forward, always

being held as close as possible to the anterior wall of the chest, the fluid is discharged into the pleural cavity. The canula is then withdrawn, and the animal is left to itself. As the incision in the skin is very small the external wound heals up very soon; generally after one or two days it is hardly to be detected. In this way the injection of any fluid and in any quantity can be effected with great ease in a very short time, and without any danger of injuring the lung, provided that the animal is kept quiet during the injection. In acute pleuritis of short duration—24 to 72 hours—the endothelium covering the pulmonary pleura shows only relatively little change. This consists chiefly in the following: the endothelial cells are more opaque and more distinctly granular than in the normal condition; now and then one meets with an endothelial cell, the nucleus of which possesses two nucleoli, and shows a more or less deep constriction. If, however, the animal is allowed to live longer than three days, it is found that many of the endothelial cells have become more polyhedral, or even short columnar, and that also their nucleus may be found in all stages of division; there are even endothelial cells the nucleus of which has divided into three small nuclei. In several rabbits, in which pleuritis had been produced by injecting septic pus, obtained from metastatic pyæmic abscesses of dogs or guinea-pigs, in the manner above described, it has been found on examining, several days after, the surface of the pulmonary pleura in horizontal microscopic sections, obtained from the lung in the moderately distended condition, that the endothelium exhibited distinct changes only at certain spots. These changes consisted in there being small groups of polyhedral granular endothelial cells amongst the common transparent flattened endothelial cells. In addition to these cells being granular, their nucleus showed more or less distinct constrictions; in other words, groups of endothelial cells are found in the germinative condition. On closer examination it was further observed that the endothelial cells of these groups were arranged more or less regularly round a common centre. Now, this centre is of the greatest diagnostic importance; either it was seen to represent a distinct hole of larger or smaller diameter, or a band of fibrin of varying thickness could be traced for a longer or shorter

distance from the free surface into that centre, so as to form a regular plug for it. The simplest explanation of the last phenomenon is, to my mind, this: the centre of the cell-group represents a stoma through which absorption is going on, and fibrin of the pleuritic exudation is found just in the condition of being pumped into that stoma. This suggestion is supported by the fact that in some instances the fibrin band can be traced into the depth for some distance.

I must mention here also the occurrence of small groups of germinating endothelial cells which apparently do not possess the arrangement above mentioned, viz. round a distinct central stoma; but here the possibility is not excluded that there is nevertheless a stoma in the centre of the group, only in a collapsed condition.

All these changes are of much greater intensity, and therefore much more distinct, if the pleuritis has become chronic. So it is found in rabbits and guinea-pigs that do not die during the acute stage, but survive this stage, and become affected with chronic pyæmia. In this latter condition the costal pleura becomes the seat of small abscesses, and so does the mediastinal pleura. The lungs both of rabbits and guinea-pigs present all the appearances of interstitial pneumonia; the lung-tissue contains numerous nodules and patches chiefly composed of round cells; they are at first firm, but gradually soften so as to form abscesses, the bronchi showing at the same time catarrhal inflammation. The bronchial glands also contain abscesses in some instances. In guinea-pigs abscesses are found occasionally also in the omentum, and then also the liver contains small nodules and large irregular patches in different stages of transformation into abscesses.

The above-mentioned germination of the endothelium around stomata is more distinct in chronic pleuritis than in acute. In Fig. 1 A I have represented these appearances; the preparation was made from the lung of a rabbit, in which chronic pyæmia had been induced after injecting into its pleural cavity a small quantity of pus obtained from a pyæmic abscess of another rabbit. The best specimens I have seen with regard to the germination of the endothelium around the stomata were obtained from the lungs of guinea-

pig in which artificial tuberculosis had been produced by injecting a very minute quantity of septic or cheesy matter of a tubercular lymphatic gland into the pleural cavity.

It is not the intention of this work to enter into a discussion of the etiology and the general anatomy of pyæmia and artificial tuberculosis in these animals, and I will only refer the reader to the well-known memoirs on this subject by Dr. Sanderson in the Reports of the Medical Officer of the Privy Council.

In artificial tuberculosis of guinea-pigs, brought on after infection through the pleural cavity, the costal and mediastinal pleura present very interesting appearances with regard to the endothelium of the surface. In many cases the pleura becomes covered with very numerous papilliform or villous processes, which, on microscopical examination, present all the characters of similar processes found on the omentum, mesentery, and parietal peritoneum, as described and figured in the First Part of this work. These villous processes are covered with germinating endothelium (see Fig. 10 in the First Part). In other cases the costal as well as the mediastinal pleura contains in its superficial parts, and projecting somewhat over the general surface, numerous nodular growths, which have also been described in the case of the peritoneum as being covered with germinating endothelium.

Somewhat different from this, however, we find the pulmonary pleura. This membrane shows in artificial tuberculosis, at most, groups of germinating endothelium on the surface. As may be expected, these groups are generally in close relation to the stomata of the surface. In artificial tuberculosis of long standing, provided the disease had been induced through the pleural cavity, the germination of the endothelium spreads over extensive areas. In these the endothelial cells are found to be larger, more columnar, and their nucleus in the act of division or already divided into two or three small nuclei. In B of Fig. 1 a group of such germinating endothelial cells is represented as viewed from the surface; the individual cells, being nearly columnar with rounded tops, appear, when viewed from above, as if separated by broad spaces. It may be noticed at the same time that each cell contains two or three

small nuclei, whereas the normal endothelial cells contain each only one large vesicular nucleus. Besides these changes, the pulmonary pleura of guinea-pigs suffering from artificial tuberculosis of long duration and induced through the pleural cavity, contains very often nudular growths, which, as we shall see, stand in an intimate relation to the lymphatics. In these cases there are always found more or less numerous places where the germination of the endothelium around the stomata appears to extend also in the depth, *i.e.* into the intermuscular lymph-spaces previously referred to; that is to say, one can find places where cells possessing all the characters of lymphoid cells may be traced from the surface, *i.e.* from among the germinating endothelial cells into the intermuscular lymph-spaces, which latter are more or less filled with them. To these appearances, however, we shall have to return hereafter.

In the course of chronic pyæmia in rabbits and guinea-pigs that have been infected by injecting the septic matter into the pleural cavity, as well as in the course of artificial tuberculosis of guinea-pigs infected through the same place, the pulmonary pleura itself becomes the seat of inflammatory changes. Especially in guinea-pigs this takes place simultaneously with the development of nodular or patch-like growths, situated in the superficial parts of the lung itself. These inflammatory changes (of the pulmonary pleura) consist (*a*) in thickening of the matrix of the pleura, (*b*) in hypertrophy of its muscles, and (*c*) in certain changes of its lymphatics. All these changes are seen to take place over greater or smaller areas, corresponding more or less to those nodular or patch-like growths of the superficial parts of the lung. Where, in the course of the disease, these latter increase in number and size, the areas of inflamed pleura also enlarge.

(*a*) The thickening of the matrix of the pulmonary pleura consists, in the earlier stages, in an infiltration with lymphoid cells; later on, the matrix is seen to contain considerable masses of fibrillar connective-tissue bundles, between which the lymph-canalicular system and its lining connective-tissue cell-plates are very well seen (see Fig. 4). The former contains also, here and there, a lymphoid corpuscle,

The fact is, the connective-tissue matrix of the pulmonary pleura has become simply thickened, otherwise its structure has not undergone any marked change. From this one may be allowed to conclude that the increase of fibrillar connective-tissue in the matrix of the pulmonary pleura stands perhaps in a genetic relation to those lymphoid corpuscles that are found to infiltrate the pleura in the earlier stages.

(*b*) the hypertrophy of the muscular coat of the pulmonary pleura of guinea-pigs is, perhaps, the most characteristic feature. This hypertrophy consists in the bundles of unstriped muscles becoming thicker, and being therefore situated nearer to one another. As the morbid process advances, the muscular meshwork, described in the First Section, may, over extensive areas, become transformed into an almost continuous muscular membrane, in which the original meshes have become reduced in number and size. This is well seen in horizontal sections through lungs, the superficial parts of which contain extensive pneumonic changes. Transverse sections through such parts show that the pleural muscles have become increased to such an extent that they form, in many parts, a continuous membrane, the thickness of which reaches that of three or four muscle-cells. In Fig. 2 I have represented a part of the pleural muscular coat in chronic inflammation (A), and in the normal condition (B). I need hardly say that Fig. A, *i.e.* that representing the morbid condition, is taken from a part where the muscular coat was relatively only slightly hypertrophied. The meaning of the hypertrophy of the pleural muscles in chronic diseases of the lung is very obvious. It is a well-known fact that obstacles which prevent certain organs or parts of organs from carrying out their normal function, produce, when assuming a chronic character, hypertrophy of the muscular tissue of those organs, if the muscular tissue take an essential part in carrying out their function. Hypertrophy of the muscular wall of the heart, or of a part of the heart, hypertrophy of the muscles of arteries, hypertrophy of the intercostal muscles, of the sterno-cleido mastoideus, &c., are well-known examples of hypertrophy of muscular tissue, caused by chronic obstacles in the organs of circulation and respiration. The nodular growths in the tissue of the lung of

guinea-pigs, which, as we have mentioned, appear in the course of chronic pyæmia and artificial tuberculosis, are evidently great obstacles to the act of respiration of the lung; and to find the pleural muscular coat hypertrophied is what we should expect, from knowing that it is of importance for the respiratory movement of the lung. Besides this there exists also another reason why the muscular coat should become hypertrophied. We shall see presently that certain portions of the lymphatics of the pulmonary pleura undergo morbid changes, in chronic pleuritis that had been induced by infecting the animal through the pleural cavity. In the course of these changes the lymphatics are less permeable, becoming, in fact, filled with the products of chronic inflammation. Now, the pleural muscular coat being to a great extent of material service to the free discharge of the lymphatics of the pleura (see First Section), it is important that its action should increase, and that it should in consequence hypertrophy, if the discharging of the lymphatics become more difficult; and this is obviously the case when they become filled excessively with formed material.

(*c*) In the First Section we have mentioned on several occasions that, in chronic pleuritis, the intermuscular lymphatic spaces of the pleura of the lung of guinea-pigs, and some of the subpleural lymphatic vessels, contain lymphoid cells. In some places these vessels are seen to be perfectly plugged up by such cells, and hence they resemble cords composed of lymphoid cells, the endothelial wall of the vessel ensheathing these cords being, however, still clearly discernible. The question arises, where do these lymphoid cells originate? There can be little doubt that the germination of the endothelium surrounding the stomata on the pulmonary pleura gradually extends to the endothelium of the lymphatics into which those stomata lead, and it is therefore quite possible that some of the lymphoid cells found in the lymphatics are direct products of that germination. Many of the lymphoid cells, however, are probably not of this origin, but are either pumped in from the exudation of the pleural cavity, or are absorbed from the tissue of the pleura itself; in both of which cases they are probably connected with the emigration of blood corpuscles—the result of the general inflammatory condition. That

in some places the lymphoid cells filling the lymphatics have nothing to do with the germination of the endothelium of the lymphatics, is proved by the fact, that in those places, neither the endothelium of the surface of the pleura, nor that of the lymphatics, shows any marked alteration. Some of the lymphatics of the pleura which are filled with lymphoid cells stand in a very close relation to the nodular and patch-like growths of the superficial parts of the lung itself, as mentioned above. The fact is, there are branches of lymphatics, filled with lymphoid cells, which indirectly take part in the formation of these growths. The reader will remember that the lymphatics of the pleura take up capillary branches originating in the alveolar septa of the superficial parts of the lung. Now, if one of those nodular growths is examined in an early state of development, *i.e.* in a lung in which there are only a few small nodules, and which otherwise shows no signs of advanced morbid changes, it will be noticed that each nodule is composed of a meshwork of more or less broad trabeculæ, and of corresponding smaller or larger spaces. The trabeculæ are seen to be composed either solely of lymphoid cells or of a tissue resembling adenoid tissue, *i.e.* a reticulum of fibres, in the meshes of which are contained lymphoid cells. Where the trabeculæ appear to be composed solely of lymphoid cells, they possess something like a bordering endothelial wall, thus resembling a tube whose wall is an endothelial membrane and whose lumen is filled with lymphoid cells. These structures can be traced very distinctly up to the branches of the subpleural lymphatics. From this it is very probable that the trabeculæ are the interalveolar rootlets of the subpleural lymphatics, partly filled with lymphoid cells, and partly already converted into cords of adenoid tissue. In later stages the conversion of lymphatic vessels, at first only filled with lymphoid cells, into cords of adenoid tissue, can be made out also in branches of the subpleural plexus itself; and in these it is found that the adenoid reticulum is in direct continuity with the original endothelial wall of the lymphatic; that is to say, that the original endothelium of the lymphatic grows as a reticulum of fine fibres between the lymph-corpuscles filling the lumen, and thus converting the vessel into a cord of adenoid tissue. In the First Part of this work such adenoid cords

and nodules, formed within lymphatic vessels of the serous membranes under normal and pathological conditions, have been described as *endolymphangial* follicular structures. In Fig. 7 I have represented lymphatic branches of the subpleural flexus filled with lymph-corpuscles and in connection with interalveolar rootlets, in some of which the conversion into cords of adenoid tissue may be noticed.

The meshes contained in the plexus of trabeculæ, which form the bases of those nodular or patch-like growths, are evidently the alveolar cavities; each of these contains, in the earlier stages, cells which from their appearance may be confidently assumed to be changed epithelial cells lining the alveolar cavities; for not only do they possess a nucleus perfectly resembling that of an epithelial cell, but their arrangement, size, and shape makes them quite different from everything else. In later stages some of these cavities are filled with cells very much resembling lymphoid cells.

Nodular growths, similar to those described just now, are found in great numbers and of different sizes in the superficial parts of the lung of guinea-pigs suffering from artificial tuberculosis. The more advanced this morbid process is, the greater their number and the larger they are. At first they appear to the naked eye as rounded grey transparent nodules; later on, as they increase in size, they become of a more irregular shape, and at the same time their centre becomes opaque, being in fact converted into a cheesy necrotic material. As the nodule grows still larger, the central caseation extends in all directions towards the circumference, as may be seen in sections cut both horizontally and transversely. Thus, nodules and patches may be found of different degrees as regards the relation between the outer progressive zone and the central caseous part. As long as these nodules are in a progressive state, they cause a slight elevation of the general surface of the pulmonary pleura, whereas this latter becomes more depressed during the process of caseation. At the same time it may be observed that the thickening of the connective-tissue matrix, as well as that of the muscular coat of the pleura, is the greater the more the process of caseation advances.

Changes in the lymphatics of the pulmonary pleura have been more recently noticed also by Debove [21] and Charcot in carcinomatous

eruptions on the pleura, subsequent to carcinoma mammæ. These authors found, that the lymphatics of the pulmonary pleura contained carcinomatous masses, which increase at the expense of the endothelium of the lymphatics. Hillairet[22] and Raynaud[23] likewise describe general lymphangitis of the pleura and the lungs in connection with carcinoma ventriculi. The latter author mentions, that the inflammatory products contained in the lymphatics are offsprings of the endothelium. Cornil[24] asserts, that in lymphangitis of the lung, which he found associated with visceral syphilis, the endothelium of the lymphatics undergoes inflammatory changes characterised by swelling and germination.

CHAPTER VII.

CHANGES OF THE LUNG PROPER IN ARTIFICIAL TUBERCULOSIS OF GUINEA-PIGS.

As is well known, the lung of most guinea-pigs affected with artificial tuberculosis (on this *see* Dr. Sanderson 'On the Communicability of Tubercle by Inoculation,' Tenth Report of the Medical Officer of the Privy Council for 1867, and Dr. Wilson Fox 'On the Artificial Production of Tubercle,' London, Macmillan & Co., 1868) is found to contain a new growth, which by many observers is regarded as very similar to miliary tubercle of man. The macro- and microscopical character of this new growth is described by Dr. Sanderson thus :—

'The new growth either assumed the form of disseminated nodules, or pervaded the tissue of the lung to such an extent that considerable portions of the organ were consolidated. There was, however, evidently no essential difference between the two forms of lesion, for in those cases in which the induration was continuous in some parts it was constantly observed that there were disseminated nodules in others, and that the material of which the nodules were composed was identical in all its characters with that which formed the larger masses. . . .

'The nodules, when examined with the naked eye or with a lens, present great uniformity of appearance. They are always found in much greater numbers under the pleura than in the parenchyma of the lung. The sub-pleural surface of each nodule is slightly convex, so that it projects more or less above the general surface of the pleura, exhibiting itself as an iron-grey patch, which contrasts strongly with the pink-white hue of the healthy lung-tissue which

surrounds it. When the nodules are small the whole sub-pleural surface is convex, but in the larger nodules the centre of the patch is somewhat depressed, so that the margin forms an irregular annular prominence. . . .

'The colour of the nodules is sometimes pale grey, but much more frequently it is steel-grey or slate-coloured, especially towards its margin; and on section it exhibits a similar colour. The smaller nodules have the semi-transparent appearance which is recognised as a characteristic of miliary tubercle. In the larger ones the translucency is confined to the external parts, the centre being opaque and of softer consistence than the rest. . . .

'Although . . . the greater number are superficial, there are many which occupy central positions, and these . . . are invariably found in the neighbourhood of bronchi. . . .

'The disease always originates in the form of minute granulations, each of which . . . is situated around or in the immediate neighbourhood of a minute bronchiole, usually a bronchiole of three or four thousandths of an inch in diameter. On more minute examination, it is found to consist in the main of adenoid tissue, that is a tissue resembling the pulp of the cortical substance of a lymphatic gland. . . .

'At first the new growth is confined to the immediate neighbourhood of the bronchioles, from which it extends to the walls of the adjoining air-cells; here it gives rise to a general thickening of the alveolar membrane, and consequent reduction of the capacity of each alveolus, and consolidation of the affected part. . . .

'Eventually the diseased part becomes completely consolidated. This is brought about partly by the interstitial growth of cells in the substance of the alveolar walls, partly by the accumulation of epithelium in the alveolar cavity. Whether by compression of the ultimate bronchus, or for other reasons, the epithelium collects in the vesicles, already reduced in size by the parietal thickening, so as to fill them up. In this way . . . the diseased tissue is converted into a compact mass of cells, which, to the unpractised or careless observer, seem to have no special arrangement, and to be all of the same kind; if, however, they are more critically examined, it is soon seen that

there are two kinds of cellular elements, those of the one kind being at least twice as large as the other, and that the larger cells are grouped together in nests. These nests correspond to the cavities of alveoli, and are, in fact, clumps of alveolar epithelium. They are distinguishable from the others not merely by their size and well-defined outline, but by the fact that most of them contain minute black pigment granules. . . .

'The next stage in the morbid process consists in the fatty degeneration of the whole mass. It is this disintegrative change which gives rise to the appearance of white or yellowish opacity always observed in the centres of the larger nodules. Both the epithelial cells and the parietal new tissue alike participate in it. . . .'

In the course of his inquiries[25] Dr. Sanderson ascertained that there are normally masses of adenoid tissue in the wall of bronchioles, as has already been referred to in the second chapter; so that the granulations which have been spoken of previously as being found around the bronchioles in the earlier stage of the disease are, in fact, only the pre-existing structures in a hyperplastic condition. At the same time, Dr. Sanderson[26] finds that the semi-transparent nodules, which have been so often compared with miliary tubercles, are not so analogous to these as to blocks of lobular catarrhal pneumonia. 'They owe their transparency not to the structural elements of tubercle, but to cells identical in size and appearance with the natural alveolar cells of the lung. . . . In animals killed at an early stage of tuberculosis, that is to say, about four weeks after inoculation with tuberculous matter, no change is observed excepting that the peribronchia adenoid pulp is increased, or, in other words, that true miliary granulations are formed in the neighbourhood of the terminal bronchioles. This fact appears to afford the key to the mode in which the iron-grey nodules are produced. Whether the choking up of the air-cells is a merely mechanical result of the accumulation of adventitious matter around the bronchioles or of a catarrhal process, there can, I think, be little doubt that the granulation stands to the block of lobular pneumonia in the relation of cause to effect, and that when a kernel of adenoid pulp occupies the centre of a nodule the fact signifies that the nodule originated from it.'

Dr. Wilson Fox[27] after having spoken of the macroscopical appearance of the miliary granulations permeating the lung of guinea-pigs that had been tuberculised, describes the microscopic characters of those granulations in this manner: 'There are three main points in which they appear to originate. One of these is around the bronchi, another is around the blood-vessels, and another is in the tissue of the lungs, where no particular connection can be seen with either bronchi or vessels. Around the bronchi they seem to extend from little masses of a lymphatic character, which normally exist in the bronchial sheath, and which are abundant in the guinea-pig. . . .

'The other place in which they commonly originate is in the perivascular sheaths of the pulmonary arteries. Here the growth appears to be nothing more than an accumulation of the cells lining the perivascular canal. The growth may extend for a considerable distance in length along both the peribronchial and perivascular sheaths; and from both these sources of origin a rapid extension ensues into the surrounding walls of the alveoli and smaller bronchi. A thickening of these is thus produced, and apparently by a double mode of growth, by a rapid development of fusiform cells at the margins, clusters of which are seen passing among the capillaries, and by an increase of rounder cells which are seen nearer the centre. Coincidently with this growth a change of great importance occurs in the capillaries of the lungs. Their nuclei enlarge, and the vessels, otherwise apparently unchanged, contain no more blood.'

Thus it is seen that there exist certain important differences between the assertions of these two authors. Whereas Dr. Sanderson distinguishes between peribronchial granulations (hyperplastic normal adenoid tissue), and semi-transparent miliary nodules (blocks of lobular catarrhal pneumonia), Dr. Fox regards all granulations permeating the lung as analogous in appearance and in their structural character, being all semi-transparent and composed of lymphatic tissue. And besides, there is this additional difference, that Dr. Fox describes the perivascular position of many granulations, which, to judge from the description, are comprised in the peribronchial ones of Dr. Sanderson.

I have quoted so extensively from Dr. Sanderson's and Dr. Wilson

Fox's papers, because I think they have entered into the appearances of the lung in artificial tuberculosis of guinea-pigs more fully, and because they have had a much greater number of these cases under their observation than other observers.

Hering,[23] who, writing on the subject of artificial tuberculosis more recently, does not seem to have been very successful in his experiments, having in fact obtained a disease more like chronic pyæmia than what is called artificial tuberculosis, finds that 'the nodules of the lung are in all cases due merely to circumscribed foci of inflammation. They were never seen to be similar to typical miliary tubercle, *i.e.* a structure which takes its origin from connective-tissue, consists of small cells similar to white blood-corpuscles, and softens first in the centre.'

With regard to my own researches on the process of artificial tuberculosis in the lung of guinea-pigs I have to state, first of all, that one may already, on superficial observation, distinguish two kinds of granulations in the lung of a guinea-pig that is considerably advanced in the process of artificial tuberculosis—say whose bronchial glands have become already the seat of caseation. The one kind comprises nodules of a spherical, or ovoid, or conical, or irregular shape; the other kind comprises granulations which have only apparently a nodular form, for on closer examination it is found that their true shape is that of a cord, and only in real or optical transverse section simulate the appearance of a nodule. All these structures have the common character that in their early state, *i.e.* as long as they are small—from a pin's head to twice and three times as large—they present a more or less transparent or semi-transparent appearance. As the process of tuberculosis advances, and the granulations increase in size, it is found that only in some of them the centre undergoes caseation, *i.e.* becomes opaque, whereas in others there is nothing of this to be seen on naked-eye inspection. As a general rule, the granulations on and near the surface of the lung are those that show first the necrotic change of their centre, which change spreads in the same manner as the granulations increase; this has been mentioned already previously. The necrotic

change is gradually established in all the semi-transparent granulations of the superficial parts of the lung. In the depth of the lung there are only few granulations, the central parts of which become the seat of a retrograde change. It may be noticed on careful dissection that the nodular shape is possessed by the granulations on and near the surface, and also by some in the depth of the lung. The latter may be seen to be of two kinds, when examined in a thick vertical section through the lung of an advanced case, under a low magnifying power; first, most of the nodules of the surface correspond to consolidations of a more or less distinct conical shape, having its basis on the surface, and its apex, or that part corresponding to the apex, directed towards the depth; secondly, farther away from the surface the nodules have either an irregular shape, or they are of a spherical or oblong shape.

Both the superficial nodules and the deep irregular ones, when magnified, are seen to possess very indefinite outlines, becoming, in fact, gradually blended with the surrounding healthy parts. The spherical or oblong nodules that we mentioned just now, possess, on the other hand, a well-defined outline; and besides, they are always in connection with the wall of a bronchiole, as will be described hereafter. They are quite different also in their structure from the first-named granulations. As a further difference I have to mention that, as far as I have been able to ascertain, only the first kind of nodules, viz. the conical and irregular ones, become the seat of the necrotic changes, *i.e.* caseation; the well-defined ones, viz. those in connection with the bronchioles and bronchi, do not undergo such a change. Nor have I ever seen the cordlike granulations, which I mentioned previously, undergo the necrotic change; at least, not in lungs which—to judge from the size and number of the granulations, the extent of consolidation, the changes in the bronchial glands and other viscera—were considerably advanced in the morbid process. By saying this I do not question for a moment the possibility of all kinds of granulations being liable to undergo the process of caseation, as asserted by Dr. Sanderson and Dr. Wilson Fox; what I maintain is, that in ordinary cases, which are not too far advanced, only the one kind of nodules undergoes the necrotic

change—noticeable as an opaque centre in the semi-transparent structure; whereas the other kind of nodules, viz. the peribronchial ones and the cordlike granulations, do not undergo such a change. When discussing the microscopical characters and the mode of growth of these different granulations, we shall be able to state that such a change, if at all, may take place only in a very advanced period.

To summarise what has been said: the granulations of a lung, which is so far advanced in the process of artificial tuberculosis that the bronchial glands have undergone already necrotic changes, may be distinguished into three kinds; (*a*) nodules of a more or less well-defined outline, being in connection with the wall of a bronchiole, (*b*) cordlike structures, and (*c*) nodular structures of a conical or irregular shape. All these three kinds of granulations are of the peculiar semi-transparent aspect; only the third kind undergoes a cheesy transformation, marked as an opacity in the centre.

Two important questions present themselves: first, what is the structure and development of these granulations? and secondly, what is their relation to one another with regard to the different stages of the morbid process?

(*a*) The spherical or oval nodular structures that we find in connection with the wall of the bronchial tubules are completely analogous to the lymphatic follicles found in the normal condition, and minutely described in Chapter IV. We have mentioned there that the adventitia of some of the bronchioles contains true lymphatic follicles, either in the shape of well-defined spherical follicles provided with a special system of blood-vessels, or of cords of adenoid tissue; and that both are in intimate connection with the wall of one of the peribronchial lymphatic vessels; and further, it has been stated that in the normal condition there is a continuous growth and new development of such adenoid tissue in connection with those lymphatics. Now, with regard to the process of artificial tuberculosis, a simple comparison of a tuberculous with a normal lung shows that in the former the number and size of those peribronchial lymphatic follicles is far greater than in the latter, and this is the more so the farther the morbid process becomes advanced. I am, therefore, at one with Dr. Sanderson and Dr. Wilson Fox, in saying that in

artificial tuberculosis the peribronchial lymph-follicles become hyperplastic; but I must differ from the assertions of the first author materially, by maintaining that this hyperplasia does not form the first change in the process of artificial tuberculosis, nor is it the inducing cause of the development of those semi-transparent nodules which, according to this observer, represent blocks of lobular pneumonia. For I am confident that in the earlier stages of the disease such a hyperplasia cannot be made out, although other marked changes can be stated already; and what is still more, according to my experience, the process of artificial tuberculosis may have made considerable progress before a marked hyperplasia of the lymph-follicles can be confidently asserted; at any rate there may exist already by that time numbers of those semi-transparent nodules which, as we shall see hereafter, have the character of lobular pneumonia.

In lungs in which the process of artificial tuberculosis has made such progress that extensive parts of the lung have become consolidated, it is found that in middle-sized bronchi, say those that still possess cartilage, the lymph-follicles have become increased in size and number to a considerable extent; there may be found, in a longitudinal section through such a bronchus, several large follicles at one spot; they are sometimes seen to become confluent. This is especially easily recognised on the smaller bronchioles, where masses of adenoid tissue may start at several distinct points, and as they increase in size, gradually approach each other and finally become confluent. In transverse sections through such bronchioles these latter are seen to be almost completely ensheathed in adenoid tissue.

I have never seen the peribronchial lymph-follicles undergoing the cheesy transformation, perhaps because I have not seen animals sufficiently advanced in the morbid process. I am, however—from certain reasons to be stated hereafter—disinclined to think it probable that the peribronchial lymph-follicles undergo spontaneously such a change.

(*b*) The granulations of the second kind—viz. the cordlike structures—are, as has been already stated, likewise of a semi-transparent appearance. On microscopical inspection they may be confused very

easily with nodules, for they appear as such whenever they are seen both in optical or real transverse section. On microscopical examination, however, their true shape can be ascertained easily, from their bearing always a definite relation to a blood-vessel, surrounding it like a sheath, as we shall see more minutely below. Hence it is quite clear that whenever such a cord is cut transversely, also the blood-vessel to which the cord belongs will be found to be cut transversely; and likewise where such a cord is seen in real or optical longitudinal section, also its blood-vessel will be seen in its longitudinal axis, and *vice versâ*. This definite relation to the vascular channels is naturally of great importance in determining whether in a given case we have before us a nodular or cordlike structure; for, if we find a granulation which, under the microscope, presents the appearance of a more or less circular structure in connection with a blood-vessel cut transversely, then it is probable that we have to do merely with the transverse section of a cord; whereas we shall judge it correctly to be a real nodule if we find it in connection with the longitudinal section (real or optical) of a blood-vessel. There are, however, real nodules found in connection with blood-vessels, some of the cords mentioned above possessing occasionally a lateral swelling of a nodular shape.*

Now, what are the general characters of these cords with regard to their distribution, structure, and development?

Their principal character is, that they bear always a definite relation to the minor branches of the pulmonary artery or pulmonary vein, being situated, as it were, in the adventitia of these vessels. For the most part the vessel is seen to be completely ensheathed by the new-growth, or, as it happens occasionally, the new-growth extends chiefly along one side of the blood-vessel. The earlier the case is the more these perivascular cords are found to be limited only to the smaller branches of the pulmonary vessels; and it seems to me—though I am not quite certain on this point—limited rather to the

* Some explanation is required for my using the term nodule for expressing a spherical-shaped body, that of cord for one that is extending in length for some distance, and that of granulation for either. The use of the latter term in the sense implied, although strictly not different in its meaning from nodule, may be readily excused by bearing in mind that on macroscopical inspection all those structures seem to be of a similar form.

smaller branches of the pulmonary artery than to those of the pulmonary vein. In later cases the perivascular cords extend also on the middle-sized branches and now pretty equally on those of the pulmonary artery as well as of the pulmonary vein. By this time it is not unfrequently found that a perivascular cord shows at one or more points of its course a smaller or larger spherical or oblong enlargement. In advanced cases the perivascular cords extend so far up the larger branches of the pulmonary vessels that they reach the point where the latter join the bronchi; here the perivascular cords come in contact with the peribronchial granulations, with which they even blend to a greater or smaller extent.

All the perivascular cords show a uniform structure, being composed of adenoid tissue, or at all events of a tissue that resembles it in almost all the principal parts, viz. the matrix is composed of fibres, including here and there a nucleus, and forming a network, in the meshes of which are situated lymphoid corpuscles. In ordinary sections of hardened specimens they have the same appearance as other lymphatic tissues, viz. as if they are made up almost entirely of nuclei; on closer inspection it can, however, easily be ascertained that the nuclei belong to lymphoid cells, and that these are held together by a fine reticulum of fibres. At an early stage of this inquiry I have been of opinion that the perivascular cords are, like the peribronchial lymph-follicles, provided with their own capillary blood-vessels, originating from the vessel to which the cord belongs. I have, however, on more careful examination become uncertain about this being really the case. There is no doubt that in advanced cases in some places the perivascular cords and their nodular outgrowths possess capillary vessels in their peripheral parts; but whether these vessels are merely the residues of the vascular system of those parts of the healthy lung into which the perivascular cords have extended in the course of their growth or not, is difficult to decide. At any rate there is a difference between the perivascular cords and the peribronchial lymph-follicles in respect of the blood-vessels; for the latter possess, as has been stated previously, their distinct system of blood-vessels (see Figs. 8 and 18).

The point of principal importance to us is that of the development of the perivascular cords. In order to study this, it is naturally necessary to begin the examination with early cases. Once acquainted with the appearances presented by the perivascular cords in their earliest stages, one is able to find similar appearances also in cases further advanced. Now, what are these appearances?

In a former chapter mention has been made of the fact that in artificial tuberculosis the perivascular lymphatics are found to be distended and filled with plasma and lymph-corpuscles (see Figs. 14, 15, 16, and 21). According to my experience, this represents the first step towards the formation of the perivascular cords. For it is not difficult to find other places where more or less numerous fibres—at some points provided with a nucleus—are seen to be in connection with the endothelial wall of those lymphatics (lymph-vessels as well as lymph-spaces), and to extend into the lumen of the lymphatic between the lymphoid cells contained in it. But also outwards, *i.e.* into the surrounding interalveolar tissue, such fibres are seen to penetrate. At some places, especially where the number of lymphoid cells contained in the lymphatic is not a large one, the number of fibres coming off from the endothelial wall is very limited, so that the meshes formed by their anastomosis contain relatively large groups of the lymphoid cells; whereas in other places, in which the development has farther advanced, the fibres have become so numerous that their network quite resembles that of adenoid tissue in its density, their meshes having only a very limited number of lymph-cells. As has been stated already, the perivascular cords in the earlier stages represent true adenoid tissue ensheathing the minor branches of the pulmonary blood-vessels to a various extent, and I have very little doubt that the perivascular cords in general develop in the manner mentioned above, *i.e.* the perivascular lymphatics become filled with lymphoid cells, between which, and in connection with the endothelial lining of those lymphatics, a reticulum of fibres makes its appearance, thus converting the lymphatics into cords of adenoid tissue. We have here before us that kind of structure which, in the First Part of this work, I termed endolymphangeal cord. With the very same thing we have become acquainted at the

beginning of this chapter, when speaking of certain changes of the subpleural lymphatics. We have mentioned there, that in artificial tuberculosis of guinea-pigs certain nodular structures are found near the pleural surface of the lung, in connection with whose development lymphatic vessels are seen to change into cords of lymphatic or adenoid tissue. On the same occasion I have expressed it as probable that most of the lymphoid cells contained in the lymphatics are emigrated colourless blood-corpuscles, and I must maintain the same also for the perivascular lymphatic cords. I have two reasons for this assertion: first, the endothelial lining of the lymphatics, in which the lymph-corpuscles are contained, does not show such marked changes as one would expect to find if the latter had originated from that endothelium; thus it becomes very probable that they (the lymph-cells) have not developed *in situ*; that they have been carried into the lymphatics from the surrounding tissue becomes probable if we bear in mind, secondly, that the alveolar septa of the adjacent parts—*i.e.* those parts in which lie the radicles supplying the perivascular lymphatics—are found invariably to contain similar lymphoid cells.

Many of the blood-vessels become thus ensheathed in lymphatic tissue, which at first appears only as a collection of lymph-corpuscles within the perivascular lymphatics, and afterwards possesses a stroma consisting of a network of fine fibres which, as has been said above, are in connection with the original endothelium of the lymphatics.

Perivascular lymphatic tissue may, however, originate also in another way. We have previously mentioned: first, that collections of lymph-corpuscles are found not only within the perivascular lymphatics, but also in the adjacent tissue outside them; and, secondly, that the fibres growing in connection with the endothelium of the perivascular lymphatics extend also into the surrounding tissue. By this means a perivascular cord encroaches on the surrounding tissue, *i.e.* grows in thickness. In the same manner an existing perivascular cord may become provided with irregular or spherical swellings. A careful examination of the lung of the earlier stages of the process (four to six weeks) shows many appearances illustrating these points. Now, the second way in which perivascular adenoid tissue makes

its appearance is the one based on the facts mentioned just now, viz. growth of a network of fibres between a collection of lymph-corpuscles lying outside a lymphatic vessel, as it were, in the wall of the latter. In Fig. 16 a branch of the pulmonary artery is represented (the character of its muscular coat, mentioned in the first section, is well shown), in the adventitia of which several lymphatics are seen, some of them containing in their lumen a granular material, and in their wall a collection of adenoid tissue.

With appearances similar to these we have become acquainted already in the First Section, in the case of the peribronchial lymph-follicles. We may therefore regard this kind of perivascular adenoid tissue as perilymphangeal tissue in opposition to the perivascular cords of the first kind, which, as we have seen, originate as endo-lymphangeal structures.

It is quite clear that the mode in which a perivascular cord becomes developed can only be determined in the earlier stages; in those cases in which the lung has advanced considerably in the process of artificial tuberculosis, so that many of the branches of the pulmonary vessels have become surrounded by great masses of adenoid tissue, it is impossible to say in which of the two ways the latter have originated; all that one can say is that they are perivascular. I refer the reader to Fig. 22, taken from a lung that contained very large and numerous masses of adenoid tissue; they are either peribronchial nodules, as in the lower part of the figure; or they are in connection with the wall of a perivascular lymphatic, as in the right part of the figure; or they are distinguishable simply as perivascular cords with nodular swellings. Besides, it must be borne in mind that a perivascular adenoid cord having originated as an endo lymphangeal structure may increase in size by encroaching on the surrounding tissue after the principle of the perilymphangeal structures.

There is one more important point to be discussed with reference to the perivascular cords. According to Dr. Sanderson, the hyperplasia of the peribronchial lymph-follicles constitutes the first series of changes of the lung in artificial tuberculosis; subsequent to, and caused by them, is the lobular pneumonia, to which the semi-transparent nodules owe their origin. To these statements I

have to add: first, there can be little doubt that Sanderson identified peribronchial and perivascular masses of adenoid tissue, otherwise I cannot account for the absence of the latter in his description; and secondly, I doubt whether the hyperplasia of the peribronchial lymph-follicles is in the earlier stages of the disease sufficiently marked to be recognised.

In a subsequent page we shall have opportunity to mention that the semi-transparent nodules which are due to catarrhal pneumonia depend on the spreading of the perivascular cords.

If, as I think to be the case, Sanderson did not distinguish the perivascular cords from the peribronchial lymph-follicles, then both those statements become explicable, viz. the hyperplasia of peribronchial follicles being the first change, and the blocks of catarrhal pneumonia being dependent on the former; for, according to my observations, the appearance of the perivascular adenoid tissue forms the earliest symptom of the process of artificial tuberculosis. Not only do we find it relatively the more abundant the earlier the stage of the morbid process is in which the lung is examined, provided, of course, that this latter possesses granulations already discernible by the unaided eye; but in most of the tuberculous lungs I have examined the perivascular new-growth is in all stages by far the most predominant feature.

The most important argument, however, I find in the fact that there are cases of artificial tuberculosis in guinea-pigs, (liver, omentum and spleen being chiefly affected) whose lungs contained miliary granulations, due *only and exclusively* to perivascular cords of adenoid tissue; the peribronchial lymph-follicles are developed only slightly in these cases, not more than in the normal condition; and further, I have seen a case of 'natural' tuberculosis in a guinea-pig, where the spleen and the liver, and likewise the lungs, but not to such an extent as the former organs, were penetrated by numerous very minute miliary granulations. The mesenteric glands were distinctly, the liver, spleen, and lung only slightly, enlarged. In the lung the 'miliary granulations' were found to be due *entirely* to the presence of perivascular adenoid cords. Fig. 20 is taken from this lung.

In connection with the changes which give rise to the development of the perivascular adenoid tissue, we have to mention changes that take place in the blood-vessels themselves. One of the very early changes in the lung of tuberculous animals is germination of the endothelium of the ultimate branches of the pulmonary artery. The endothelial cells of smaller or larger areas are seen to be enlarged, their substance being granular, and their nucleus in the act of division or already divided into two small nuclei. The germination of the endothelium may, later on, be so extensive that the inner coat of the vessel becomes lined with several layers of cells which, nearer towards the lumen, resemble young or lymphoid cells. I have seen small arterial branches in which the germination of the endothelium had reached such an extent, that of the lumen of the vessel only a very narrow canal was left, not broader than the diameter of a coloured blood-corpuscle; just above this stenosis the vessel was considerably distended.

In the larger branches of the pulmonary vessels also the other coats of the vessel undergo abnormal changes in a more advanced stage of the disease. These changes consist in the coats of the vessel —especially the middle coats—becoming very distinctly laminated, the individual laminæ being separated from one another by clefts which contain the more numerous lymphoid cells the farther the diseased stage is advanced. In arteries possessed of a thick middle coat this condition is especially well seen. The lymphoid corpuscles can be seen to extend into the coats of the vessel from without—*i.e.* from the perivascular cords. There is *à priori* no reason why this should not be due to an active growth of the tissue of the perivascular cords into the walls of the vessel; the microscopical examination presents a great deal of evidence in support of this. One of the strongest points in favour of it is the fact that there are arterial as well as venous branches in such a relation to the perivascular cords that at certain points the proper coat of the vessel appears to be completely supplanted by the morbid tissue, so that this latter nearly comes in contact with the lumen of the vessel.

In one of the following pages we shall again see that the perivascular cords extend gradually also into the interalveolar tissue, and

thus produce a considerable increase of thickness of the alveolar septa. Under those changes the ultimate capillary vessels distributed in the alveolar walls suffer to a greater or smaller extent. First of all there is to be observed an increase of the nuclei belonging to the wall of the capillary vessel, as had been already signalised by Dr. Wilson Fox, mentioned at the beginning of this section. But it does not stop there, for at some places capillary vessels are seen to be continuous with solid threads, containing nuclei completely resembling the nuclei of the capillary. These nucleated threads are of a slightly granular appearance, and are in continuation with the fibres of the tissue of the thickened alveolar septa. Besides the reasons just mentioned, there are others which support the view that these nucleated threads are transformed capillary blood-vessels. They are the following: 1. A capillary vessel is occasionally seen whose lumen terminates almost abruptly as a cuneiform space, whereas its wall is directly prolonged into a nucleated thread. 2. In preparations of lungs that had been injected with cold solution of Berlin blue, the injection material is found not to stop altogether at those cuneiform endings of the capillary vessel, but to extend also on the solid threads; at least these are either stained distinctly blue, or they possess a row of blue granules.

The question arises now, in what relation do the changes of the blood-vessels, described above, stand to the process of artificial tuberculosis? That the changes of the capillary blood-vessels, as occurring in the later stages, have only a secondary importance, being subsequent to the morbid changes of the alveolar septa, will, I think, be readily admitted on all sides. The question turns only on the changes described in the wall of the ultimate branches of the pulmonary artery, occurring in the earlier stages of the disease. The fact that such changes are found at a very early period, *i.e.* at a period when a limited amount of perivascular new-growth can be recognised; and further, the fact that changes in the wall of minor branches of the pulmonary vessels are met simultaneously with the development of small masses of perivascular adenoid growth around the same vessels; these two facts, I think, tend to show that the changes in those vessels stand in an intimate relation to the de-

velopment of the perivascular masses. The strength of this argument is, however, weakened to a certain extent by the recent observation I have made, to the effect that in a case of 'natural' tuberculosis of a guinea-pig there were no distinct changes to be found in the minor branches of the pulmonary blood-vessels, although most of them were ensheathed in adenoid cords.

(*c*) The third kind of semi-transparent 'granulations'—which, as has been mentioned previously, are found abundantly in the superficial parts of the lung, and are of an irregular, occasionally of a more or less distinctly conical shape—owe their origin to catarrhal pneumonia, as correctly indicated by Sanderson. At the beginning of this section we have mentioned briefly their structure, having stated that they are composed of trabeculæ and spaces; the former representing the thickened alveolar septa, the latter being the alveoli and filled with products of the alveolar epithelium. The trabeculæ are in direct connection with perivascular cords; in fact, the tissue of the latter is seen to encroach on the alveolar septa, whereby they become thickened. They seem to be composed of fibres, and include numerous lymphoid corpuscles. The reader will no doubt remember, from a previous description, that the thickened infiltrated trabeculæ of the superficial semi-transparent nodules stand in direct continuity with superficial lymphatics, the lumen of which has become replaced by cords of adenoid tissue. The same relation between the trabeculæ and the lymphatic cords exists in all granulations of this category.

With regard to the abnormal contents of the alveolar cavities in these structures, the examination of the earlier stages proves that it consists entirely of alveolar epithelial cells and their derivatives. To convince oneself as to this, it is sufficient to study attentively any good preparation illustrating a very early stage—*e.g.* one represented in Fig. 24. We find here that the adenoid tissue forming the perivascular cord *c* (cut transversely) encroaches on the interalveolar tissue; that is to say, that this latter shows similar structural elements to the former, both forming at the same time a continuity. The epithelial cells lining the alveolar cavities are seen in most places to

be only loosely attached to the alveolar wall. Speaking roughly, they may be distinguished as three different kinds of cells: first, we find, besides very scarce lymphoid bodies, recognisable by their small bright nucleus, epithelial cells which differ from the normal elements merely by being somewhat enlarged, distinctly granular, and containing occasionally a constricted nucleus, or even two nuclei, like the cells at *d*; secondly, epithelial cells considerably enlarged, more or less irregular in shape, and containing always several nuclei, which generally lie more or less near the central part of the cell; and thirdly, masses of granular protoplasm of considerable dimensions and irregular in shape, containing numerous nuclei irregularly distributed through the cell-substance—*i.e.* giant cells, as at *e*.

A careful examination leaves no doubt that all these elements are of an epithelial nature; for not only are their nuclei so characteristic that already by that alone they may be distinguished from the lymphoid elements in the walls of the alveoli, but chiefly the presence of the numerous intermediate forms enable us, as it were, to trace the one category into the other. It is not unusual for many of these cells to contain minute black particles, which, as has been pointed out by Knauff in his very able paper, are merely carbon particles. The most interesting features are, no doubt, the multinuclear giant cells. Some of these are seen to extend over a considerable distance, and to fade away at one or the other point of their outline into a very transparent film. Their nuclei (12 to 20 and more) are relatively small; many of them contain two nucleoli, and are hour-glass or kidney-shaped or otherwise constricted, thus showing distinct signs of division. The important question arises now, how do these giant cells originate? That multinuclear protoplasmic masses originate by the excessive growth of one of those epithelial cells, containing several nuclei, can be taken as very probable from the fact that one finds transitional elements from the one to the other. But also another mode of the formation of these giant cells must be admitted, and that is by the fusion of *several* epithelial cells. I am inclined to think that the largest giant cells originate in this manner; for almost all of them show in one or the other portion of, or all through, their substance more or less distinct markings, *i.e.* outlines

of the individual elements, by the fusion of which the giant cell has originated. It is of great importance to notice, where the giant cell shows these markings, *i.e.* where its substance shows a faint indication of being divided into territories, that to each of the latter belongs a nucleus, which is generally larger than any of those nuclei that lie irregularly scattered through that part of the giant cell that does not exhibit those markings. Hence it is very probable that several epithelial cells become gradually fused together, and while this fused protoplasmic mass continues to grow, the nuclei of the original cells undergo division, and become irregularly distributed through the cell substance. There exists, as far as I can see, no difficulty in assuming that the giant cells are, like other growing cells, able to perform amæboid movement—their irregular shape certainly does suggest this—and that they are able to take up other smaller elements. This last assumption may perhaps be taken as supported by the fact that not unfrequently the giant cell contains one or two small nucleated cells, either sticking simply in a peripheral portion of its substance or suspended in a larger or smaller spherical cavity, i.e. in a vacuole. The latter appearance may, however, be due to endogenous cell-formation. I am not in a position to decide which of the two is the true explanation.

The changes of the alveolar epithelium, in consequence of which, as had been stated before, the alveolar cavities become more or less filled, bear, according to my experience, a definite relation to the perivascular cords. For not only do we find those changes taking place where the tissue of the perivascular cord encroaches on the alveolar septa of the surrounding parts, in consequence of which they (alveolar septa) become considerably thickened, but—(and this I think is of still greater importance)—these changes of the alveolar epithelium become the less marked the farther away from the perivascular cord. This is evidently the reason why the semi-transparent masses of the third category—viz. those corresponding to blocks of catarrhalic lobular pneumonia, or to 'lobular foci of desquamative pneumonia,' as Buhl calls them—possess, when examined under the microscope, rather indefinite outlines, the morbid parts merging more or less gradually into the surrounding healthy tissue.

In advanced cases of artificial tuberculosis the catarrhal changes spread from the alveoli on the infundibula and smaller bronchi. In the latter the germination of the lining epithelium may reach such a degree that the lumen of the air tubule becomes, for some distance, almost completely blocked up by several layers of nucleated cells of a polyhedral shape. Amongst these the intraepithelial connective-tissue corpuscles—i.e. the pseudostomatous tissue described in the First Section—are seen to penetrate in great abundance.

As may be expected from the compression and degeneration of the blood-vessels, the products of the catarrhal process finally undergo fatty degeneration and necrosis, i.e. caseation. This process starts, as a rule, from the cell-masses that fill up the alveolar cavities, and while spreading gradually involve also the thickened interalveolar trabeculæ. I have seen advanced cases where the lung contained several caseous masses of pyramidal shape, and showing on section racimose markings. Their basis reached almost the pleural surface, and their apex was represented by one of the larger bronchi. This latter and all its tributaries were replaced by the necrotic material, and hence the racimose markings.

In several cases I have seen extensive parts of the lung becoming consolidated without cheesy transformation. The tissue of these parts was represented by an almost uniform reticulum of nucleated cells with very numerous and finely branched anastomosing processes. I first thought this tissue takes its origin from the alveolar contents of the inflamed parts; after a more careful examination, however, I became much more inclined to think that it is due to an excessive development of the interalveolar tissue, the epithelial cells of the corresponding alveoli being gradually made to disappear, and the alveoli themselves becoming more or less permeated by that reticulum.

CHAPTER VIII.

ACUTE MILIARY TUBERCULOSIS IN MAN.

To enter into the recent literature of the histology of miliary tubercle of man is far beyond the scope of this work, especially as this subject has been fully treated of in the well-known works of Waldenburg, Langhanns, Rindfleisch, E. Wagner, Klebs, Köster, Schüppel, T. Hering, Friedländer, and others. In the present chapter I will be content with describing the structure and development of miliary tubercle of the lung, occurring in the disease known as *acute miliary tuberculosis.*

Before doing so I will venture to quote certain passages [29] from Buhl's admirable work, which contain a short, and I believe a fair, account of the histology of miliary tubercle in general.

Buhl writes thus: 'With regard to its histology especially, E. Wagner has established a closely-meshed network (reticulum, reticular tubercle), containing in its meshes cellular elements, the size and number of which increase from the periphery towards the centre.

'Fresh young tubercles contain, however, two distinct kinds of fibres. 1. Peripheral dense tracts of *connective tissue*, arranged circular and parallel; in them one recognises the small spherical shining nuclei of cells. 2. Continuous with 1, and extending towards the centre, is the *proper reticulum*, which, from want of nuclei, I do not regard as connective-tissue, but as a homogeneous connective-substance. . . . I have never been able to detect true nuclei in it. It is also neceesary to mention that the substance of the reticulum is the softer the younger the tubercle; in fact, the reticulum is altogether wanted in the first rudiment of the tubercle, and hence the cells are found closely situated to one another.

'Also the cells (embedded in that matrix) are of different kinds. I distinguish—1. Cytoid bodies, situated chiefly in the peripheral connective-tissue zone. . . . They and their nuclei are smaller and brighter than those of blood and lymph corpuscles. . . . 2. Large so-called giant cells (Langhanns), consisting of finely granular protoplasm, provided with branched processes, and containing numerous nuclei grouped together in the centre. It is beyond doubt that the plenitude of the nuclei is due to division. The nuclei are spherical or ovoid, nearly of equal size—at any rate, larger than those of lymph-corpuscles—and consequently also larger than the nuclei of the previously mentioned cytoid bodies.

'The giant cells lie in the centre of the reticulum. Occasionally there is only a single one; or, if there are several, the one that lies in the very centre is the largest. It may be compared to the mother-cell of the tubercle. The more recent observers, when describing the characters of tubercle, have justly attached some importance to the presence of the giant cells; but Schüppel evidently overrates them in representing them to be a constant and, save expressing it, a specific feature. . . .

'3. Besides the cytoid bodies and giant cells, the tubercle contains cells of an epithelial character, which, to judge from their size and position, represent, as it were, the intermediary forms between the former two. Their protoplasm is bright, finely granular, and surrounded by a membrane. They contain one large nucleus, or several small nuclei, which resemble here those of the giant cell, there again those of the cytoid bodies.

'I do not doubt that they are of the same nature and origin as the giant cells. . . .

'The smaller giant cells are the largest cells of this kind. . . . They occupy the meshes of the reticulum around the giant cells; they diminish in size the nearer they are to the peripheral connective-tissue zone (in the same way also the reticulum becomes denser), and appear to pass insensibly into the cytoid bodies in the same manner as they do into the giant cells on the other hand.

'As long as the tubercle grows, the nuclei of the giant cell continue to multiply, and the number of cells around it increases.

Hence the reticulum becomes enlarged, and the peripheral connective-tissue zone thickened by the increase of the corpuscles embedded in it.

'This augmentation is, however, very limited, lasting only for a short period; for its substratum being very soon exhausted, the giant cell perishes, partly by fatty degeneration, partly by becoming hard and horny and forming occasionally laminated concretions (Schüppel). The other cells of the reticulum comport themselves in a similar manner; they undergo fatty degeneration. But the cytoid bodies contribute to the hypertrophy of the connective-tissue zone, which draws closer and closer round the degenerated central cells.'

With regard to the origin of the giant cells, Buhl summarises (p. 101) thus:—

'E. Wagner has . . . thought himself justified in assuming that they (giant cells in the liver) result from a multiplication of nuclei of the liver-cells. . . . (According to Colberg from a multiplication of the nuclei of capillary blood-vessels.) . . .

'Most commonly it is believed that the cellular elements of the connective tissue give origin to the giant cells, and hence also to the tubercular lymphoma. The assertion of Langhanns that out of spindle-cells are formed protoplasmic masses in which only nuclei are produced, has great weight. Whereas, in the formation of normal lymphoid organs, or in their enlargement by normal excitations . . . only cytoid bodies are produced; abnormal excitations induce the generation of giant cells.

'The same claim is laid by the endothelium of the lymphatic sheaths of fine arteries, the endothelium of lymphatic vessels (Rindfleisch, Klebs), and perhaps also of fine veins.'

Buhl, with many recent histologists, regards all these structures as belonging to the same group of tissues, and, inferring from this, he requires 'no more than the presence, at the seat of the irritation, of *a pre-existing element of the group of connective-tissue corpuscles and endothelium* . . . out of which the lymphatic new growth (tubercle) is developed and further organised.' Buhl therefore rejects the theory of Schüppel, 'who supposes the formation of tubercle to take place most commonly within blood-vessels, and who

assumes mother-cells (Brutzellen) in the blood, which arise from coagulated fibrin, and which become surrounded by germinating endothelial cells of the blood-vessel. In this case—Buhl goes on to say—the giant cells must be derived either from colourless blood-corpuscles, which, however, as far as I know, possess no such high germinative energy,* or one of the endothelial cells of the vessel must have become greatly enlarged—which Schüppel himself does not assume, finding the germinating endothelial cells only around the mother-cells; or, finally, it is necessary to assume that protoplasmic lumps, circulating in the vascular system, are stopped in certain capillary vessels, and grow into giant cells; this is a hypothesis which could not be admitted for many practical and theoretical reasons.'

'These deductions are directed also against the doctrine of Waldenburg, . . . who maintains that capillary emboli, produced by corpuscular elements, form the nucleus of the formation of tubercle.'

Having further described the regressive changes of miliary tubercle in general, Buhl goes on to say that all this applies likewise to miliary tubercle of the lung.

With regard to acute miliary tuberculosis of the lung, Buhl asserts [30] that it 'is a *desquamative pneumonia*' (lobular catarrhal pneumonia auct.), 'which differs from the true genuine kind in so far that, among the germinating epithelium of the alveolar wall also giant cells make their appearance, and that consequently the tubercle is situated from the beginning in the cavity of the alveolus; further on also miliary tubercles become developed, by local infection, in the swollen trabeculæ, these being the seat of a new formation of connective-tissue elements.'

A similar assertion is made by Hering, who maintains [31] that 'those cases which are generally designated as acute miliary tuberculosis of the lung, and are distinguished by their rapid, commonly lethal course, are not due . . . to tuberculosis, but are caused by disseminated acute catarrhal pneumonia.'

In the same work, which, with reference to miliary tuberculosis

* This argument has lost much of its strength, after the very interesting observations of Ziegler (Centralblatt für med. Wiss. No. 51–58. 1874), who finds that true giant cells may be formed by emigrated colourless blood-corpuscles.

of man, contains a great number of very important microscopical observations, Hering remarks[32] that 'in chronological respect the reticular tubercle (Wagner's Lymphadenoma) occupies the first place; then follows the cellular tubercle, which under certain circumstances becomes transformed into the fibrous tubercle.'

With regard to the giant cells of the reticular tubercle, Hering doubts their connection with the cells of the reticulum, and believes they are not true cellular elements but[33] 'correspond most probably to lymphatic vessels cut transversely. Their finely granular substance would then be identical with the contents of the vessel coagulated by the action of the reagent, used for hardening, and the cells (nuclei!) embedded in that substance are probably only the endothelial cells of the vessel having become changed by germination.'

Having quoted extensively from Buhl's work, I shall be saved from giving a separate description of certain appearances presented by miliary tubercles of the lung found in some cases of acute miliary tuberculosis.

There are certain important points in which I venture to differ materially both from Buhl and Hering. Foremost is the assertion that in all cases of acute miliary tuberculosis, distinguishable as such in clinical and (rough) anatomical respect, the miliary tubercles are due to desquamative pneumonia (lobular catarrhal pneumonia).

This proposition I can only accept as correct if it be put so as to mean that all cases of acute miliary tuberculosis have at the beginning the character of desquamative pneumonia; for not in all cases that die from acute miliary tuberculosis are the tubercles of the lung found to be due to pneumonia, but are seen to correspond in their structure to reticular giant-cell tubercle in different stages of development. Buhl's saying that the desquamative pneumonia representing the acute miliary tuberculosis differs from the genuine desquamative-pneumonia in the presence of giant cells among the germinating epithelium of the alveoli, does not apply to all cases, but corresponds *only to a certain stage of development* of the tubercles.

I have had the opportunity of examining the lungs of seven chil-

dren that died from acute miliary tuberculosis. With the exception of one—in which the diagnosis had been uncertain whether enteric fever or acute miliary tuberculosis—all cases were well-marked examples of the disease. Two out of the seven cases were in so far distinguished that in both the lungs were permeated in all directions by very numerous grey tubercles, the outlines of which were, however, not very sharp. In the other five cases the tubercles of the lung were only of a limited abundance. In all seven cases there were tubercles on the pleura pulmonis, in the spleen, omentum, liver, and kidneys. The mesenteric glands were enlarged and congested. In clinical respect they were, with the exception of the one case mentioned before, diagnosed readily as acute miliary tuberculosis.

The microscopic examination proved that in the first two cases, just referred to, the tubercles of the lung were due to what coincides, according to Buhl's description, with desquamative pneumonia. It was, namely, found that the abnormal masses correspond to groups of alveoli (and infundibula), being filled with and distended by a fibrinous material that contains granules and small cells. Generally these latter occupy the centre of the alveoli, and are more numerous in the alveoli nearest to the centre of the tubercle. The structure of the alveolar wall is hardly distinguishable, and its capillary blood-vessels not permeable, as is shown by the fact that in well injected (artificially) specimens the injection does not extend into those capillaries. The alveoli next to the tubercle contain a similar fibrinous material, but are not filled with it completely, for their epithelium can be distinctly recognised, the individual cells being somewhat enlarged, and many of them detached. Some of the cells contain two nuclei. Into these parts the injection material did, however, penetrate; for the capillary blood-vessels of these alveoli are seen to be more or less perfectly injected. Still further away from the tubercle the alveoli contain either a small amount of fibrinous material, besides isolated young cells, or a homogeneous substance which stains faintly with hæmatoxylin. The epithelium is here very distinct, its cells granular. In some of the alveoli the epithelial membrane is found more or less detached, and the capillary blood-vessels always perfectly permeable (Fig. XXV.).

All through both lungs the nodules show the same histological characters. There was no trace of giant cells anywhere. In the spleen of the same two cases the tubercles were seen to be of a completely different character; here they were due to necrosis of the tissue of the spleen. Every tubercle contained, either in its periphery or near its centre, the residue of an arterial branch blocked up by a granular débris. The great mass of the tubercle was also a mere débris, in which, in many places, the outlines of the elements of the splenic tissue could be just descried. There were numerous tubercles, in the periphery of which giant cells of different sizes had already made their appearance.

Thus I presume the tubercular masses of the spleen in these two cases were due to necrosis of the tissue of the spleen (probably at first only that of the lymphoid tissue of the arterial sheaths), caused by embolism of the corresponding arterial branch. Those tubercles, at the periphery of which the giant cells are present, are probably those that are further advanced.

In others of the examined cases the tubercles of the lung were seen to differ in their structure from those in the former series, in the following respects:—1. In some of them there is a distinct cell-infiltration of the tissue around the nodule; this latter representing, as in the former case, a number of alveoli very much distended by fibrinous material, which includes granules and small cellular elements. 2. The trabeculæ—i.e. the interalveolar tissue of the peripheral parts of the tubercle—are slightly thickened, and contain lymphoid cells. The capillary blood-vessels are, even here, not yet completely permeable, and therefore not easy to distinguish.

The same lung contains tubercles, of which only the central portion—i.e. the alveoli situated nearest to the centre—are of the same condition as those in the first series (viz. being distended by, and filled with, fibrinous material); whereas the alveoli of the peripheral part do not contain the fibrinous material any longer, but are occupied in one or other of the following ways:—First, by spherical or irregular-shaped nucleated elements, many of which can be still recognised as epithelial cells by their size, granulation, and

nucleus. The larger ones contain two, three, and more nuclei. In these places the interalveolar trabeculæ are thickened in a very marked manner, containing amongst nucleated fibres—connected with and crossing each other—small lymphoid corpuscles, the nuclei of which stain very readily with logwood or carmine. Or, secondly, they are filled by one large multinuclear mass or giant cell. This contains the nuclei either regularly distributed in its periphery, or they are all crowded together about the central part. The nuclei stain readily, are sharply outlined, and contain one or two nucleoli; they are of different sizes, generally larger than those of lymphoid cells. The substance of the giant cell is very regularly granular, and is tinted slighly yellowish. This is especially well brought out in sections stained with hæmatoxylin. The cell-substance does not stain either with hæmatoxylin or carmine. As a rule the giant cell is embedded in, and connected with, retiform (interalveolar) tissue. Thus the appearance of a reticular giant-cell tubercle is produced, as described at the beginning of this chapter.

From the foregoing the reader has, no doubt, perceived that I hold that the tubercles of the second series—i.e. those described last—represent later stages of development of those of the first series, the fibrinous exudation filling up the alveoli gradually disappearing—i.e. being most probably absorbed by the surrounding tissue, which is in a state of increased activity, as shown by the infiltration and distended blood-vessels—and becoming replaced by groups of cells (most of them being offsprings of the alveolar epithelium), or by one multinuclear mass or giant cell. The interalveolar tissue is thickened (commencing from the periphery), and transformed into a retiform tissue, which contains also lymphoid corpuscles.

The central part of the tubercle is the one in which the fibrinous exudation disappears latest from the alveoli, and is replaced by giant cells surrounded by retiform tissue and lymphoid corpuscles; so that finally we get a tubercle which contains, corresponding to almost all the alveoli comprised in the nodule, larger or smaller giant cells surrounded by retiform tissue. Compare Fig. XXVI. and explanation of it.

That most of the former are really in anatomical continuity with

the latter by more or less numerous processes, as generally described by almost all authors except Hering—who maintains that this continuity does not actually exist, but is only apparent—can be easily proved by making a teased preparation. In this way the giant cells, together with parts of the surrounding tissue, may be isolated, and the continuity of both can be established beyond doubt.

And here I have arrived at a second point, with regard to which I must differ from Buhl's and Hering's description. It is with reference to the structure of the retiform tissue, in which the giant cells are embedded.

I have never seen that the retiform tissue surrounding the giant cell is true adenoid tissue—i.e. a delicate, almost uniform, and homogeneous reticulum, in the meshes of which are embedded, likewise almost uniform, lymphoid cells—as is asserted by Wagner and Buhl, and is figured by Hering in Fig. 2, Plate I. What I find is either a network of elongated clumsy-looking nucleated cells, the substance of which is more or less longitudinally striated, or a network of fibrillar substance, containing here and there a nucleus, or finally intermediate stages between the two—viz. where the matrix in some parts of the tubercle is more like the one, in other parts more like the other, network. Thus I perfectly agree with Schüppel, who, while opposing Wagner's view, asserts that the retiform matrix has nothing in common with true adenoid or lymphatic tissue. Also, with reference to the changes and the fate of the giant cells, I endorse Schüppel's statements, viz. that their substance gives rise to nucleated cells which help to increase the retiform tissue, and also to cells which are more or less similar in appearance to lymphoid corpuscles, and which lie in the meshes of the former. They appear to originate, in some instances, by endogenous cell-formation. Commencing from the centre of the tubercle, the giant cell as well as the surrounding tissue having been converted into a dense fibrillar substance, or, without doing so previously, degenerates, becoming firm, hard, and finally assuming the appearance of a more or less débris-like mass.

As has been stated by Buhl (see on a former page), the giant cells have been justly regarded as a very interesting and important

structure, although they are not pathognomic, and a great deal of discussion has been devoted to their origin. The reader will remember that they have been said by different observers to originate from different parts of the tissue in which they are found. Thus they have been represented to originate from nuclei of capillary vessels, from epithelial cells (liver-cells in the liver), from connective-tissue cells, from an amorphous material within blood-vessels, from endothelium of lymphatics, and, finally, it has been said (Hering) that they are not cells at all, but an amorphous material filling up lymphatic tubes.

We come now to discuss the origin of giant cells in tubercles of the lung only. With their mode of origin in tubercles of other organs we have nothing to do. I must accentuate this, as my experience teaches me that not only giant cells in general, but also those of tubercles in particular, have a different mode of origin in different organs.

Now with regard to the giant cells occurring in tubercles of the lung in, as I have endeavoured to show, *certain stages* of acute miliary tuberculosis, I presume it is evident, from a comparison of the structure of tubercle in its different stages, as described above, that there exist only two possibilities of the mode of origin of the giant cells, viz. either from lymphoid corpuscles—i.e. colourless blood-corpuscles, probably displaced from blood-vessels into the alveolar cavities in an early stage—or from epithelial cells lining the alveolar cavities. In favour of the first mode of origin is the observation of Ziegler (see on a former page), that colourless blood-corpuscles may, under certain conditions, give rise to giant cells; and the almost constant occurrence of groups of lymphoid cells, in the first stages of acute miliary tuberculosis, in the centre of the alveoli.

The second mode of origin—viz. that from alveolar epithelium—is, on the other hand, supported by a great amount of what appears to me to be strong evidence indeed. First and uppermost stands the fact that we find *all intermediate forms* between well-developed giant cells and nucleated cells of an undoubted epithelial character; secondly, the observation of giant cells originating from single epithelial cells, or from a fusion of such in the alveoli of the lung in

the semitransparent nodules that we described in the previous chapter as secondary nodules in the process of artificial tuberculosis of guinea-pigs is surely of some importance, bearing in mind that there exists a certain analogy between the tubercles of the lung in acute miliary tuberculosis of man and the semitransparent secondary nodules in the artificial tuberculosis of guinea-pigs, in both cases the changes being in an early stage due to disseminate catarrhal pneumonia. Buhl speaks of the development of giant cells from alveolar epithelium (p. 107), and thinks this is in no way incompatible with the assumption that they originate in general from a tissue belonging to the group of the connective-tissues. This I must, however, regard as an unsuccessful arbitration. Buhl, in his assumption that the alveolar cavities are lymphatic cavities, and therefore lined by endothelium, which is not belonging to the group of epithelium, strictly speaking, but to that of connective-tissues, is, as it appears from p. 5 of his work, guided by the experimental observations of Sikorsky, who, as had been mentioned in the First Section, found that carmine particles find their way from the alveolar cavity directly into the lymphatic radicals of the alveolar wall. This deduction of Buhl becomes at once untenable, if it is remembered that the relation between the alveolar cavity and the lymphatics of the alveolar wall is precisely the same as that between the lumen of a bronchus and the lymphatic system of its wall. No one can say that the epithelium lining the mucous membrane of the bronchi is not epithelium in the strictest sense, in morphological as well as in genetical respect. I have explained Sikorsky's experimental observations by the presence of pseudostomatous tissue in the wall of the alveoli, and in that of the bronchial epithelium (see Chapters IV. and V.). Buhl's conclusion has been supported to some extent by the assertion of Debove that the epithelial lining of the alveolar cavities is a continuation, not of the bronchial epithelium, but of a bronchial subepithelial endothelium. But since Debove himself has retracted[34] this assertion, it must naturally be left out altogether from the discussion.

That the giant cells of the tubercle of the lung are true cells—generally of a spherical, oblong, or irregular shape—and that they

may be isolated by teasing, of this fact I have satisfied myself repeatedly. (Compare Fig. 27.) It is also insisted upon, if I remember rightly, by Friedländer. I cannot therefore accept Hering's view that the 'so-called' giant cell corresponds merely to a granular substance filling up the lumen of a lymphatic vessel, and what is generally, and quite correctly, described as the nuclei of the giant cell to be identical with the endothelial cells (!) of that vessel. On the other hand, I have occasionally seen a giant cell of a distinct tubular shape. But this, I think, may simply mean that the giant cell has, from some reason or other, *grown* into that shape. Besides, the disposition of the giant cells in many a tubercle of the lung is in conflict with their being identified with lymphatics.

In those lungs in which the tubercles show already necrotic changes, numerous blood-vessels are seen to be surrounded by a greater or smaller amount of adenoid tissue perfectly analogous to the perivascular cords, described in artificial tuberculosis of guinea-pigs. Also in the adventitia of the bronchi spherical collections of lymphatic tissue are to be met with.

NOTES.

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2. *Wywodzoff:* Wiener Medicin. Jahrb. Bd. xi. 1866.
3. *Sikorsky:* Centralblatt f. medicin. Wiss. No. 52, 1870.
4. *Recklinghausen:* Virchow's Archiv. Bd. 36, p. 172.
5. *Ludwig and Schweigger-Seidel:* Arbeiten aus der physiolog. Anstalt, Leipzig, 1866.
6. L.c.
7. *Dogiel and Schweigger-Seidel:* Ibidem.
8. *Bizzozero:* Centralblatt, No. 14. 1874.
9. *Ranvier:* Quoted in Farabeuf: De l'épiderme et des épithéliums. Paris, 1872.
10. *Tourneux:* Journal de l'anatomie et de physiol. 1874, 66–83.
11. *Troisier:* Recherches sur lymphangites pulmonaires. Archives de Physiol. Norm. et Pathol. 1874, pp. 355–366.
12. *F. E. Schulze:* Article 'Lung' in Stricker's Manual of Histology.
13. *Burdon-Sanderson:* Eleventh report of the medical officer of the Privy Council, 1868, p. 101, 102.
14. *Axel Key and Retzius:* Max Schultze's Archiv, vol. ix. p. 308.
15. *Kyber:* Max Schultze's Archiv, vol. viii. part. iv. p. 581 and fllg.
16. *Mihalkovics:* Arbeiten aus der physiolog. Anstalt in Leipzig, 1873, viii.
17. L.c. p. 572.
18. *Buhl:* Lungen-Entzündung, Tuberculose und Schwindsucht. München, 1872, p. 5.
19. *Debove:* Comptes rendus. Décembre 1872.
20. *Knauff:* Ueber das Pigment der Respirations-Organe. Virchow's Archiv, vol. xxxix. p. 443.
21. *Debove:* Note sur les lymphangites cancéreuses. Progrès Médical, 1874, No. 6.
22. *Hillairet:* Lymphangite généralisée des poumons. L'Union Méd. 1874, Nos. 53, 54, 55.
23. *Raynaud:* Mémoire sur l'angioleucite généralisée des poumons. L'Union Méd. Nos. 35, 36.
24. *Cornil:* Note sur les lymphangites pulmonaires. L'Union Méd. No. 81.
25. *Dr. Sanderson:* On the communicability of Tubercle by Inoculation. Tenth report of the medical officer of the Privy Council, 1867, p. 118, and follg.
26. *The same:* Eleventh report of the medical officer of the Privy Council, 1868, p. 114.
27. *Dr. Wilson Fox:* On the artificial production of Tubercle. London, 1868, p. 11.
28. *Hering:* Histologische und experimentelle Studien über die Tuberculose. Berlin, 1873.
29. *Buhl:* L.c. p. 97, and fllg.
30. L.c. p. 107.
31. L.c. p. 88.
32. L.c. p. 87.
33. L.c. p. 105.
34. Travaux de laboratoire d'histologie du Collége de France, publiés par Ranvier. Paris, 1874, p. 22.

EXPLANATION OF PLATES.

PLATE I.

FIG. 1. A. Surface-view of endothelium of the pulmonary pleura of rabbit, in the condition of chronic pleuritis.

a. General flattened endothelium.

b. Germinating endothelium round stomata, these latter being plugged up by fibrinous material, stained dark by nitrate of silver.

B. Surface-view of endothelium of the pulmonary pleura of a guinea-pig suffering from chronic pleuritis (due to artificial tuberculosis produced by injection of cheesy material into the pleural cavity).

The endothelial cells being almost columnar, seem, when viewed from above, to be only loosely connected, in consequence of their tops being rounded; many cells have two nuclei or a constricted nucleus.

C. Surface-view of the same endothelium of a normal guinea-pig, the lung of which was in a collapsed condition.

D. The same seen in profile.

Hartnack, Oc. III. Obj. 7.

FIG. 2. A. Meshwork of unstriped muscles in the pleura pulmonis of a guinea-pig suffering from chronic pleuritis.

a. Intermuscular lymph-sinuses, lined by a single layer of endothelial plates.

b. Muscular trabeculæ (silver preparation).

B. The same muscle in the normal pleura pulmonis (silver preparation).

Hartnack, Oc. III. Obj. 7.

FIG. 3. Bundles of unstriped muscles, as in B of fig. 2, hardened with spirit and stained with hæmatoxylin. The muscular cells show distinct fibrillation of their substance.

Hartnack, Oc. III. Obj. 8.

FIG. 4. Matrix of connective-tissue bundles of pleura pulmonis of a guinea-pig suffering from chronic pleuritis. Surface-view, showing the arrangement of the connective-tissue bundles and the interfascicular spaces, *i.e.* lymph-canalicular system, containing the flattened connective-tissue corpuscles.

Oc. III. Obj. 10, à immersion.

FIG. 5. Longitudinal section through a small bronchus of a guinea-pig's lung.

a. Ciliated epithelium.
b. Circular coat of unstriped muscles, transversely cut.
c. Lymphatic follicles belonging to the wall of lymphatic vessels, *d*.
e. Branch of pulmonary artery.
f. Lymphatic vessels.
g. The same filled with granular material (coagulated plasm). In some of the lymphatic vessels clusters of lymph-corpuscles are to be found.

Oc. III. Obj. 5.

PLATE II.

FIG. 6. Surface-view of sub-pleural lymphatic vessels of guinea-pig injected with Berlin blue.

a. Large trunk provided with valves.
b. Branches which emerge from the depth, *i.e.* from the inter-alveolar tissue.

Oc. III. Obj. 4.

FIG. 7. Surface-view of lymphatic vessels of lung of guinea-pig suffering from artificial tuberculosis, produced by injection of cheesy material into the pleural cavity.

a. Branches of the sub-pleural plexus of lymphatic vessels.
b. Interalveolar branches. The whole system is filled with lymph-corpuscles; in some places, however, the vessel is in the state of being converted into a chord of adenoid tissue;

the vessels are provided with a membrane composed of endothelial plates.

Oc. III. Obj. 7. (Tube not drawn out.)

FIG. 8. From a longitudinal section through the wall of a bronchus of guinea-pig.

a. Ciliated epithelium.
b. Muscular coat, transversely cut.
c. Lymphatic sinus possessed of a special endothelial wall, *e*, and surrounding
d. Injected lymph-follicle.
f. Injected blood-vessel.
g. Connective-tissue adventitia of bronchus containing lymph-corpuscles.

Oc. III. Obj. 7.

PLATE III.

FIG. 9. A. Surface-view of epithelium of bronchus of rabbit, showing between the epithelial cells (viewed from the surface, and appearing therefore as a mosaic of polyhedral cells) nucleated branched cells.

B. The same seen in profile.

a. Epithelium with intraepithelial nucleated cells—Pseudo-stomatous cells in connection with
b. Nucleated cells of sub-epithelial mucous membrane.

Oc. III. Obj. 7.

FIG. 10. Diagram of a longitudinal section of a minute bronchus.

a. Epithelium.
b. Subepithelial connective-tissue corpuscles in connection on the one hand with pseudo-stomatous tissue, and on the other hand with
d. The endothelial wall of
e. Lymphatic vessel of the bronchial adventitia.
c. Muscular coat.

FIG. 11. From a transverse section through the lung of guinea-pig.

a. Alveolar cavity.
b. Lining epithelium.
c. Capillary blood-vessels, injected; they are, however, represented as if uninjected, and not nearly so numerous as in

the actual preparation, in order to make the drawing not too complicated.

d. Interalveolar connective-tissue corpuscles sending processes between the epithelial cells of the alveoli—Pseudo-stomatous tissue.

Oc. III. Obj. 7.

FIG. 12. From a section through a guinea-pig's lung that had been injected with nitrate of silver, and then frozen, in order to cut the sections.

a. Branch of pulmonary artery.

b. Lymphatic vessels in connection with

c. Interalveolar lymph-spaces, *i.e.* the lymph-canalicular system.

Oc. II. Obj. 5.

FIG. 13. A. From the same lung, showing the interalveolar lymph-spaces in the surface-view.

B. From the same lung, showing the lining epithelium of the alveoli; between them small holes—pseudo-stomatous canals. See explanation of fig. 11.

Oc. II. Obj. 5.

FIG. 14. From a vertical section through the lung of a guinea-pig suffering from slight artificial tuberculosis.

a. Branch of pulmonary artery. The arrangement of its circular muscular coat is very striking.

b. Perivascular lymphatics, probably only lymph-sinuses bordered by connective-tissue bundles lined with endothelium. These lymphatic spaces contain granular material (coagulated plasm) and lymph-corpuscles, *c*.

d. Muscular bundles transversely cut.

a'. A small branch of the artery.

Oc. III. Obj. 5.

FIG. 15. From a vertical section through an injected lung of a guinea-pig suffering from artificial tuberculosis.

a. Branch of pulmonary vein.

b. Capillaries around the alveoli.

c. Alveoli with their epithelium.

d. Lymphatics.

e. A lymphatic filled with lymph-corpuscles.

f. Perivascular adenoid tissue, either only in connection with

the wall of perivascular lymphatics, or, as in the upper part of the figure, being the lymphatic itself.

Oc. III. Obj. 7.

PLATE IV.

Fig. 16. From a section through a guinea-pig's lung (artificial tuberculosis in a slight degree), showing the development of lymphatic follicles and cords in the wall of perivascular lymphatics.

a. Artery in longitudinal section.
b. Lymphatics.
c. Lymphatic tissue (adenoid tissue).
d. Muscular coat of artery.

Oc. III. Obj. 4.

Fig. 17. From a section through a guinea-pig's lung, normal.

a. Injected branches of pulmonary vein.
b. Alveoli with their lining epithelium.
c. Perivascular lymphatics, lined by an endothelial membrane.

Oc. III. Obj. 5.

Fig. 18. Section through a larger bronchus of the lung of a guinea-pig; the blood-vessels had been injected from the pulmonary artery, the injection material (cold Berlin-blue) had escaped through the lymphatic vessels, whereby these latter had also become injected. They were not fully injected, but their wall was brought out distinctly by the adherent Berlin-blue, the lymphatic vessels being at the same time distended, as is represented in the drawing. The lung was hardened in spirit, and the preparation stained with hæmatoxylin.

In the upper part of the figure the bronchial wall is seen longitudinally from its external surface.

a. Epithelium.
b. Muscular coat.
c. A duct of a mucous gland.
d. Veins.
e. Branch of pulmonary artery.
f. Branch of bronchial artery.
g. Perivascular lymphatics.
h. Peribronchial lymphatics, both anastomosing with each other.
i. Lymph-follicle.
k. Cartilage.

Oc. II. Obj. 4. (Tube not drawn out.)

FIG. 19. From a section through the same lung as fig. 18.

a. Perivascular lymphatic, accompanying a small blood-vessel, *b*.
c. Capillary blood-vessels ramifying in the wall of the alveoli.
d. Radicles of lymphatic vessel, *i.e.* the lymph-canalicular system belonging to the wall of alveoli.
e. Nuclei belonging to connective-tissue corpuscles situated in those radicles.

Oc. II. Obj. 7.

FIG. 20. From a vertical section through a lung of guinea-pig suffering from artificial tuberculosis. The lungs contained only perivascular tuberculous cords and nodules composed of adenoid tissue.

a. Blood-vessels filled with blood.
b. Perivascular cords of adenoid tissue in transverse section.
d. Nodular swelling of the latter.
c. Alveoli.
e. Interalveolar tissue.

Oc. III. Obj. 4. (Tube not drawn out.)

PLATE V.

FIG. 21. From a section through the same lung as in fig. 20.

a. Blood-vessels in transverse section.
b. Lymphatics.
c. Alveoli.
Showing that the perivascular tuberculous cords may begin as simple accumulations of lymph-corpuscles in perivascular lymphatics.

Oc. III. Obj. 7.

FIG. 22. From a vertical section through the lung of guinea-pig suffering from artificial tuberculosis in a very high degree. (Injected lung.)

a. Bronchus.
b. Pulmonary artery.
c. Branch of pulmonary artery.
d. Perivascular tuberculous cords and nodules, as well as peribronchial lymph-follicles.
e. Lymphatic vessels.
f. Alveoli.
g. Blood-vessels of the latter.

Oc. II. Obj. 4. (Tube not drawn out.)

Fig. 23. From the same lung as fig. 22.

a. Branch of pulmonary artery in transverse section.
b. Pulmonary vein.
c. Tuberculous nodule.
d. Tuberculous cords.
Both latter contain carbon particles.

Oc. II. Obj. 4.

PLATE VI.

Fig. 24. From the same lung as figs. 22 and 23.

a. A branch of pulmonary artery, not filled out by the injection. The endothelium of the artery is very distinct.
b. Capillary blood-vessels surrounding the alveoli.
c. Perivascular adenoid tissue, representing the tuberculous cord.
d. Epithelium lining the alveoli; at *e* the epithelial cells are giant cells, taking their origin by the fusion of several epithelial cells, changed during the inflammation. There are, however, other multinuclear cells which take their origin from a single epithelial cell.
This change of the epithelium is secondary to the process of artificial tuberculosis.

Oc. III. Obj. 8.

Fig. 25. From a vertical section through the injected lung of a child that died of acute miliary tuberculosis. The figure represents about one-third of a tubercle.

a. Injected blood-vessels; they become impermeable towards the centre of the tubercle. The alveoli, nearer to the centre, *b*, are very much distended by a homogeneous or fibrinous material, in the centre of which lie small lymphoid cells—probably emigrated colourless blood-corpuscles; towards the periphery, *c*, of the nodule, the alveoli are less distended and their lining epithelium becomes more distinct.

Oc. III. Obj. 5. (Tube half drawn out.)

Fig. 26. From a vertical section through the lung of a child that died of acute miliary tuberculosis; the lung had been very successfully injected; the vessels, however, do nowhere penetrate into the tubercles.
The figure represents a tubercle of a later stage than that in fig. 25. The lung-tissue that surrounds the tubercle is not unlike adenoid tissue;

the primary alveolar cavities are occupied by giant cells, which stand in connection with the thickened alveolar septa; these latter consist for the most part of a fibrous material provided with numerous nuclei. Under a high power it is seen to consist of nucleated cells, the substance of which becomes fibrous.

Oc. III. Obj. 4. (Tube not drawn out.)

FIG. 27. From a teased preparation of the same lung as fig. 26; representing a giant cell of a tubercle, the centre of which had undergone fibrous degeneration. The giant cell lies close to the centre.

Oc. III. Obj. 8.

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Fig. I

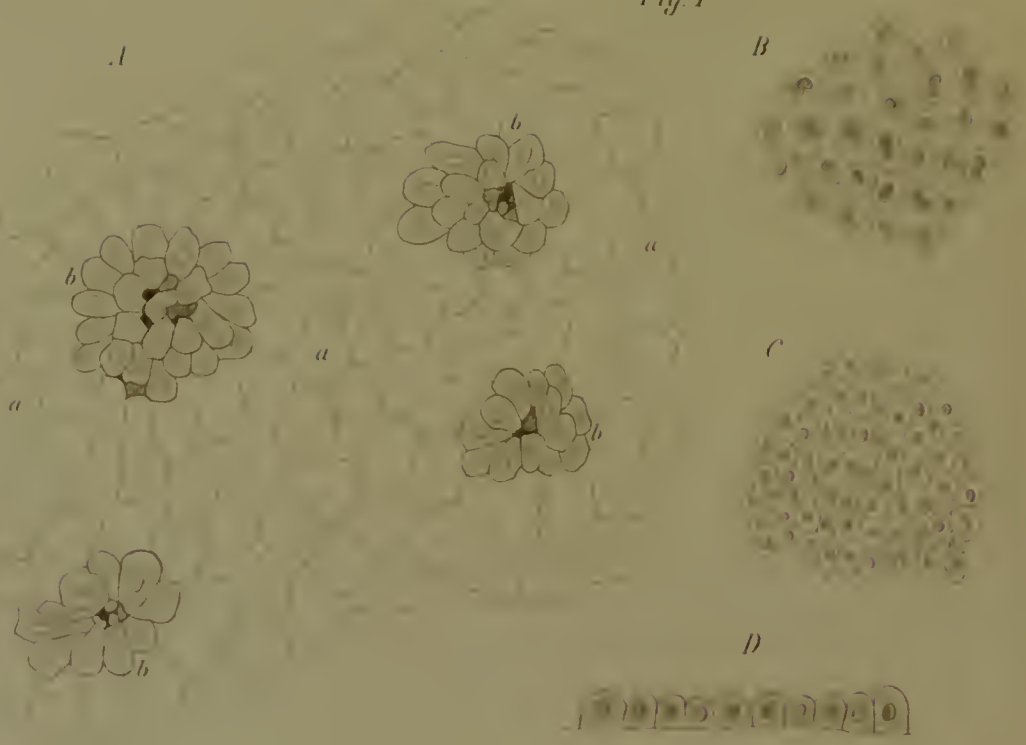

Fig. III.

Fig. IV.

F. Klein dil.

Fig. II.

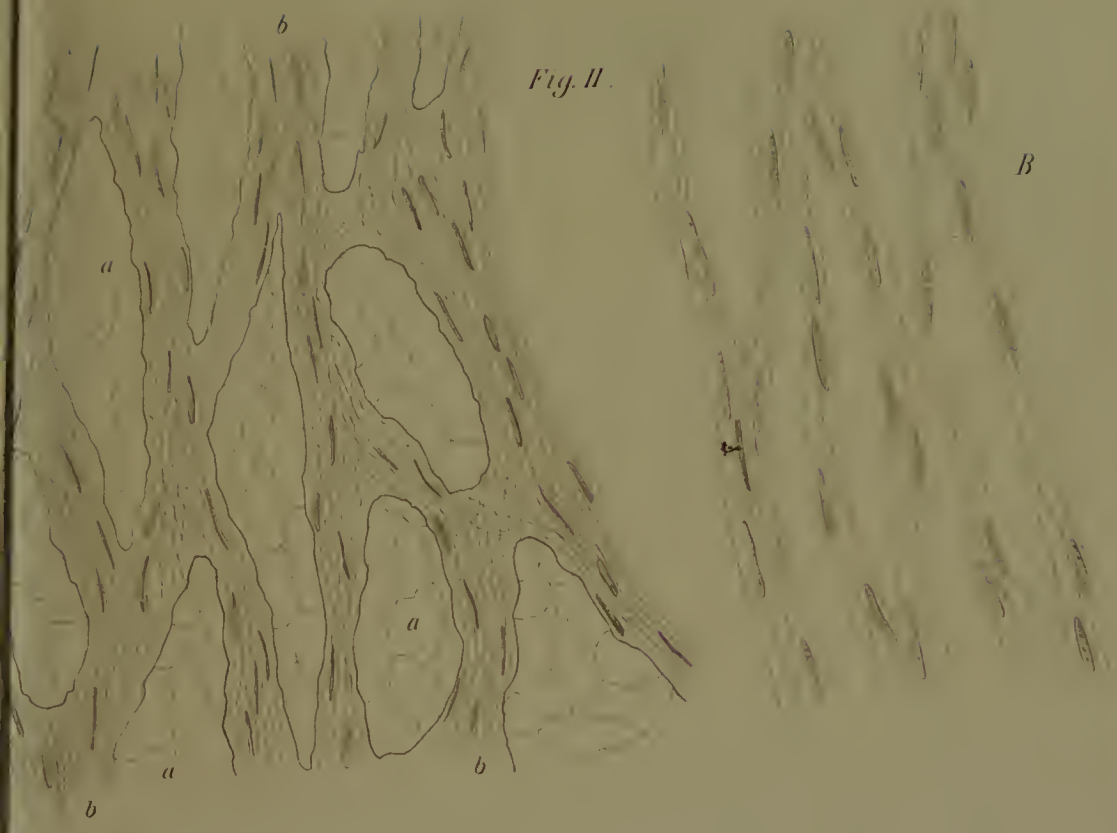

Fig. I.

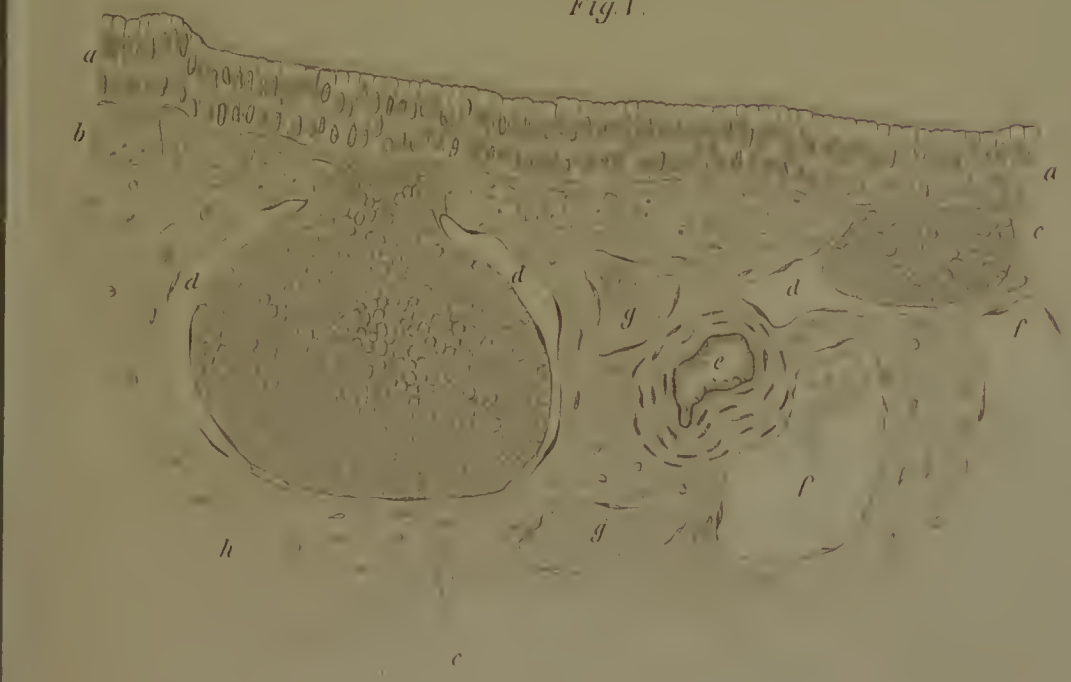

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Fig VI

Fig VII

Fig VIII

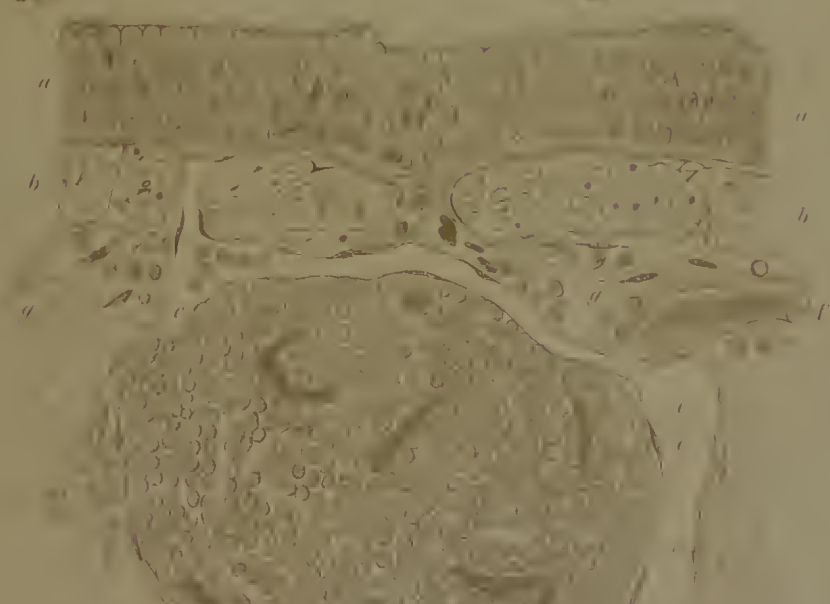

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Fig IX

B

Fig V

Fig VI

Fig VII

Fig. XII.

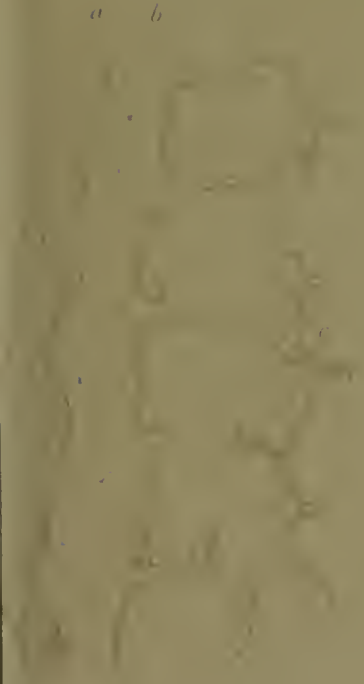

Fig. XIII.

Fig. XI

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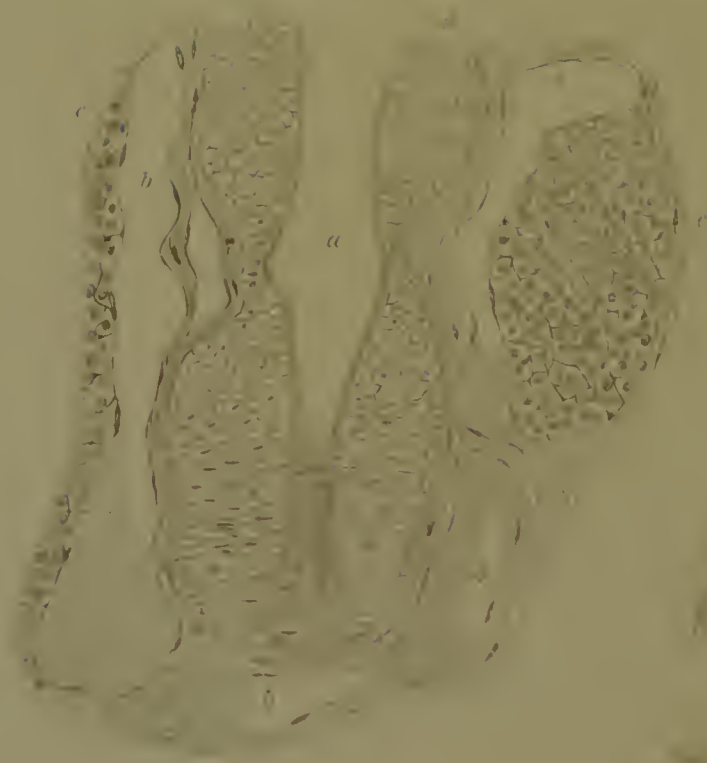
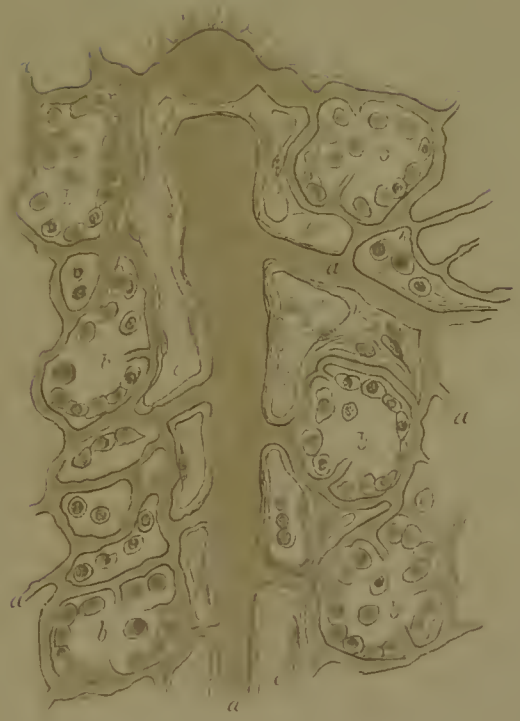


Fig. XII.

Fig. XI.



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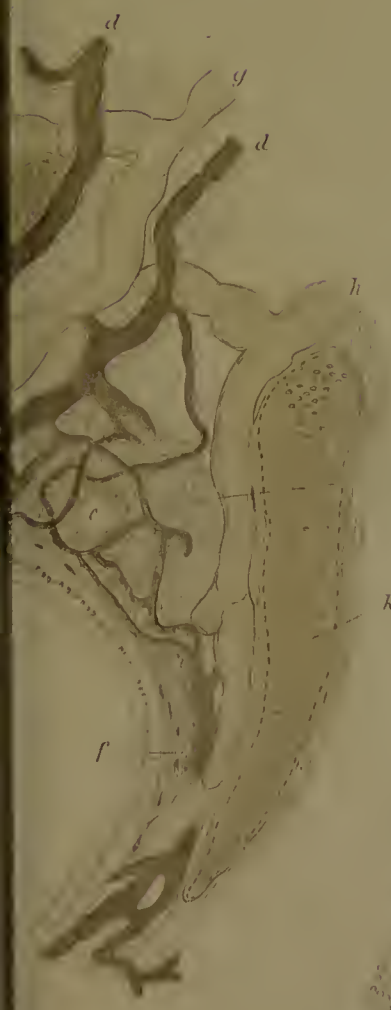

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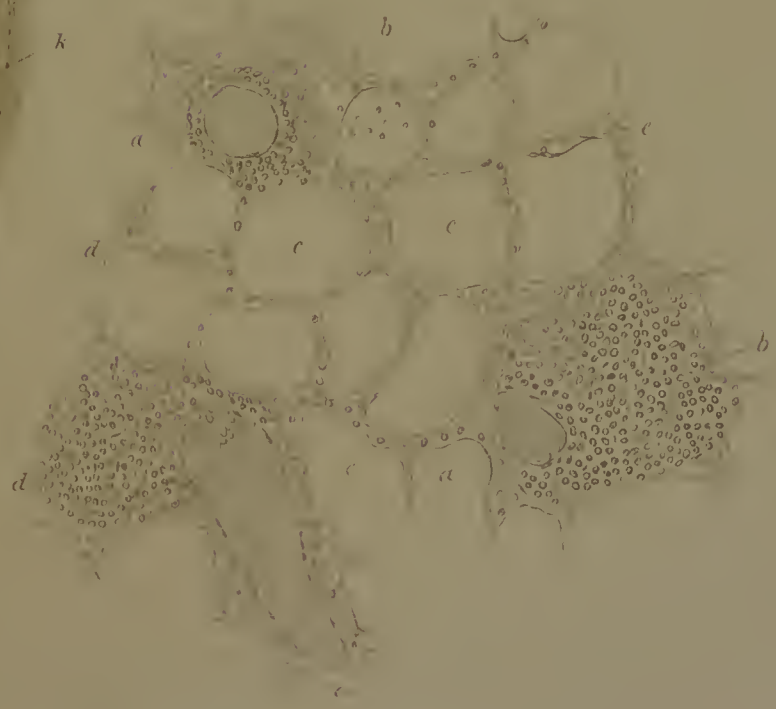

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Fig. XXI.

Fig.

F. Klein del.

XII.

Fig. XXIII.

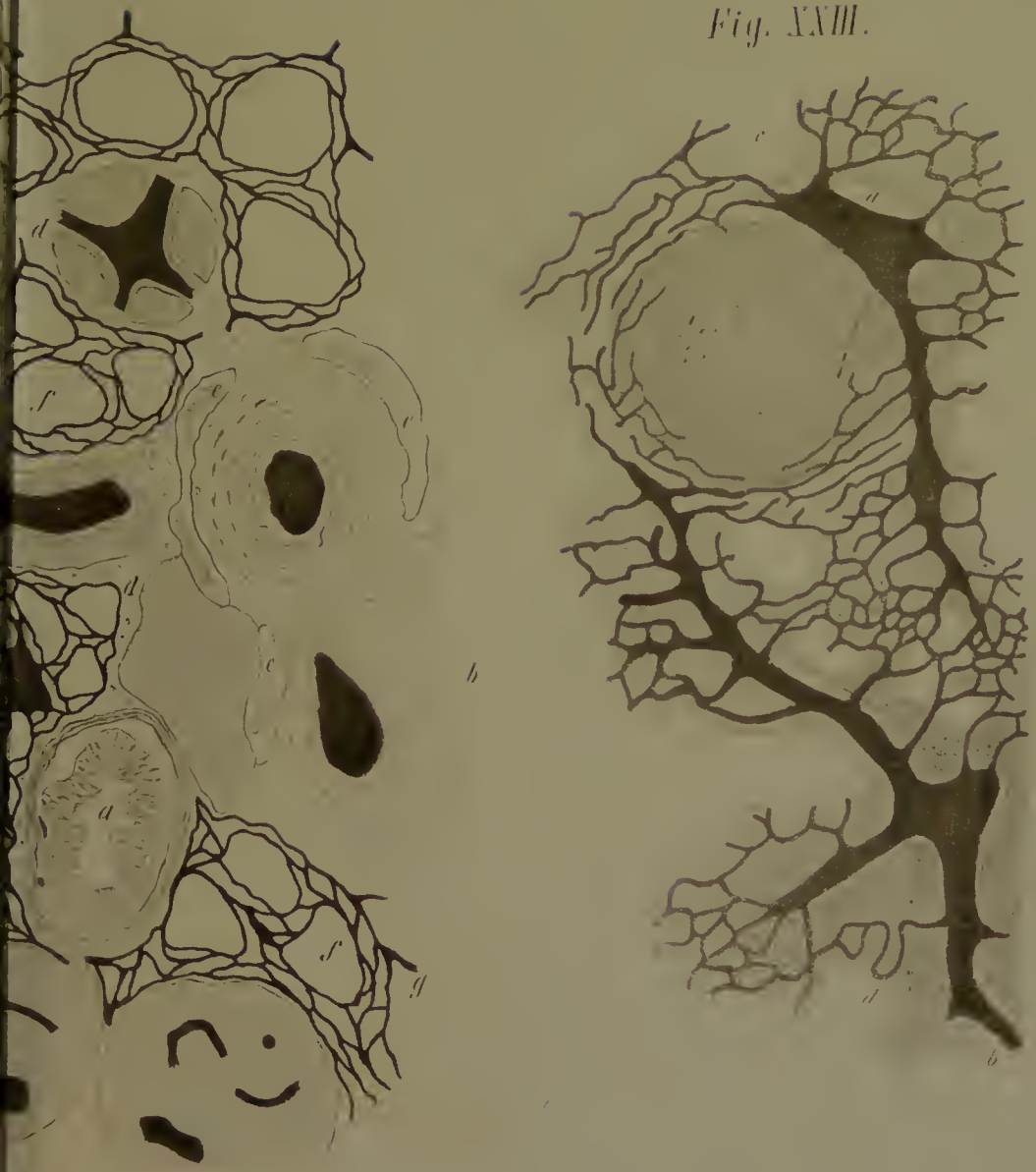

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Fig. XXV

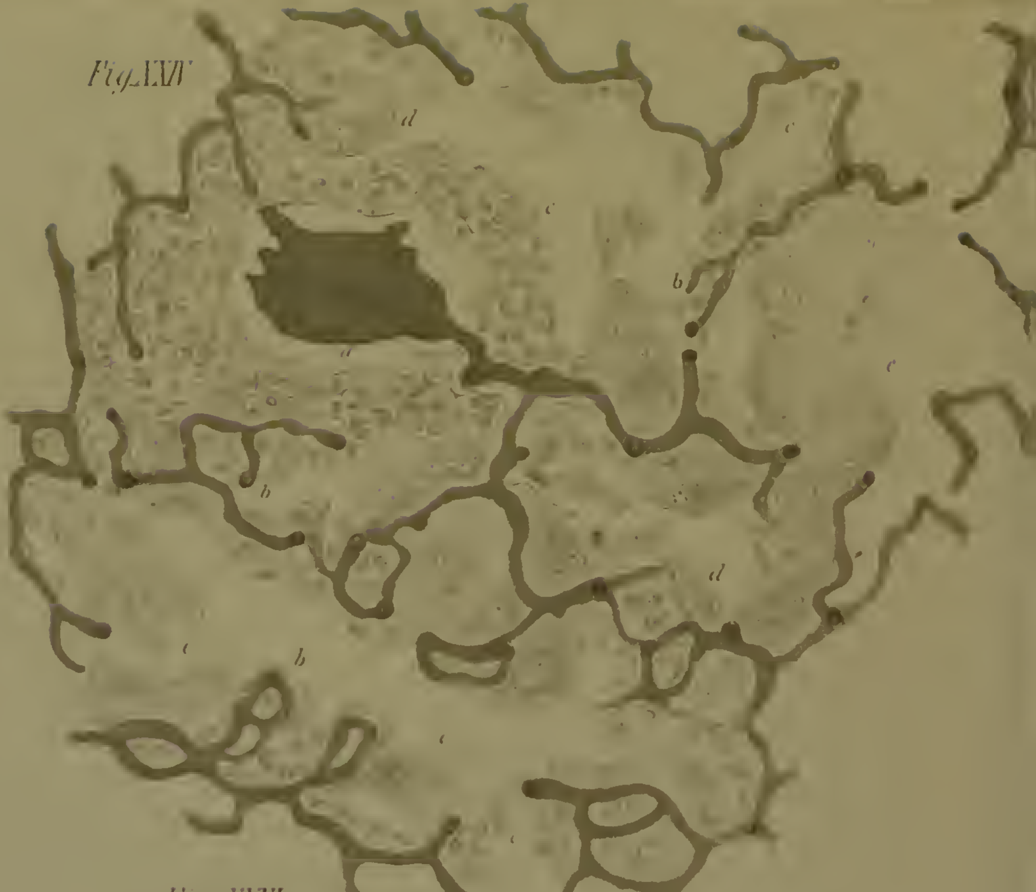
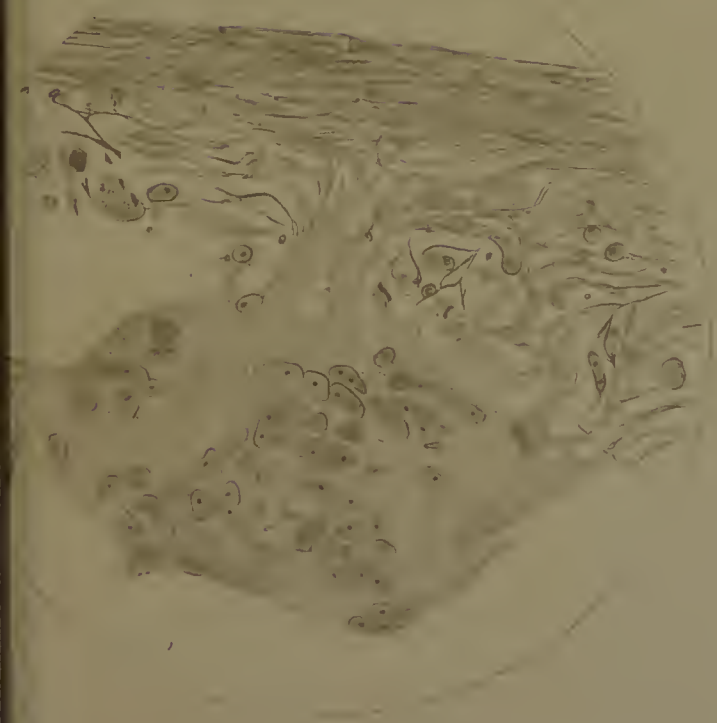


Fig. XXVI

E. Klein del.

Fig. XVI.

Fig XVII.



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